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**Washington State Pharmacy and Therapeutics Committee**
**Drug Utilization Review Board**
**December 19, 2012**

Barak Gaster: So, good morning, everybody. We are going to convene the December 19th meeting of the Washington State Drug Utilization Review Board. My name is Barak Gaster, and I think we are going to begin with a couple of quick announcements and reminders from Duane Thurman.

Duane Thurman: I just want to let everyone know that we are, as usual, transcribing the meeting from a recording, and also we have a court reporter, so please make sure that you identify yourself clearly into the microphone when we're talking, and the usual stuff.

Barak Gaster: All right, so, I'm Barak Gaster, and let's start by going around the room and giving introductions.

Nicole Nguyen: Hi, I'm Nicole Nguyen, senior pharmacist with the Health Care Authority, Medicaid.

Amy Irwin: Hi, Amy Irwin, pharmacy program manager with Health Care Authority.

Chuck Agte: Chuck Agte with Medicaid, Health Care Authority, and I'm a pharmacy administrator.

Kenneth Wiscomb: Ken Wiscomb, I'm a member of the P&T Committee.

Christine Klingel: Christine Klingel, committee member.

Eric Harvey: Eric Harvey, committee member.

Mason Bowman: Mason Bowman, committee member.

Christopher Smith: Christopher Smith, committee member.

Barak Gaster: Barak Gaster, committee member.

Susan Rowe: Susan Rowe, committee member.

Deborah Wiser: Deb Wiser, committee member.

Michael Johnson: Michael Johnson, committee member.

Po Karczewski: Po Karczewski, committee member.

Regina Chacon: Regina Chacon, Health Care Authority.

Leta Evaskus: Leta Evaskus, Health Care Authority.

Donna Sullivan: Donna Sullivan, Health Care Authority.

Duane Thurman: Duane Thurman, Health Care Authority.

Ray Hanley: Ray Hanley, Health Care Authority.

Nathan Johnson: Nathan Johnson, Health Care Authority.

Andre Rossi: Andre Rossi, DOC.

Barak Gaster: Alright, thank you very much, and this is Barak Gaster, and I want to take a moment before we get going to give a very warm thank you to Ken Wiscomb, who is here on his last meeting of a long and illustrious tenure on the committee, so thank you very much, Ken.

[applause]

Barak Gaster: I understand that we are not far away from finalizing a new member of the committee.

Duane Thurman: Correct, I hope to have an announcement out realistically in January.

Barak Gaster: Great. Alright, so now we are going to begin with a topic that is fore in everyone in this room's mind, which is healthcare reform, and Nathan Johnson who is the assistant director of Health Care Authority policy is going to give us a 25-minute update on healthcare reform.

Nathan Johnson: Great.

Barak Gaster: Thank you.

Nathan Johnson: Well thanks for the opportunity to be with you today, and I'm going to focus some of my comments today on the Medicaid expansion element, but I'm happy to address questions about health reform more broadly, and I'm actually going to try to limit the slide portion of the presentation to about 10 or 15 minutes at the most to allow some interaction time, if you have any questions about impacts, and I will try not to speak too fast in trying to get to that target, but if you have any questions or would like to interrupt at any time, please feel free to do so, but before I even go there, it is important to note that the governor did release her budget yesterday. It included the Medicaid expansion in its entirety, as well as a projection that the Medicaid expansion over the 1315 biennium would save $140 million of general fund state dollars.

In addition, and of interest, although not related to health reform to this board, the formulary was dealt within the budget. The policy continues and moves forward, but some of the savings estimates that were predicated on an early implantation of the formulary are being bought back at a maintenance level in the budget, and I just thought folks would be interested in that level of detail, so you knew what was going on in that area, and if there are any other questions HCA related on the budget, I am happy to address those. If you could advance the slide for me.

I want to start out by setting up for you what the goals of the Health Care Authority have been, as it relates to the Medicaid Expansion. Just to give you, this gives you a good, broad, I think overview and a context for the discussion. The first is to optimize every opportunity to streamline administrative processes. As many of the folks in this room know, Medicaid itself is a very complex program with many

eligibility categories, many financing mechanisms, and many holes in terms of who it covers. The Affordable Care Act offers a great way of streamlining some of our administrative processes to make it a much easier system to navigate for both the state and its consumers.

The second would be to leverage new federal financing opportunities to ensure that the Medicaid expansion is sustainable. I alluded to that at a high level, in terms of what the budget estimates indicate. A lot of the savings from the Medicaid expansion is as a result of refinancing existing state obligations with, at least in the early years, 100% federal financing for the Medicaid elements.

Maximizing use of technology to create a consumer-friendly application, enrollment, and renewal experience. The application renewal process for consumers today and for the state is onerous. It takes a lot of time and in some cases errors are made, appeals and the like. The opportunity to leverage the new health benefit exchange eligibility portal is an incredible one. We are talking about a real-time eligibility experience where someone can walk in for 20 minutes, enter their information, automatically source federal and state data hubs to determine whether their income information is correct and determine them at that point in time eligible for either Medicaid or tax credit subsidies in the Health Benefit Exchange. We will talk in a little bit more detail, as time allows on that topic.

Fourth, to maximize continuity of coverage and care, as individuals move between the coverage options. This is important, because the problem we have today, especially around the Medicaid program, is many times people turn off coverage when their income circumstances improve or if they forget to renew or don't go through the paperwork or what have you, they turn off of coverage in its entirety, and it's only when that medical need re-presents itself potentially that they come back into coverage.

The new problem created in the Affordable Care Act is a good problem, near universal access to coverage, but what it's done is we have a Medicaid program and an exchange where different health plans will be offering different products and different provider networks. So, as people's circumstances change, there's going to be churn, and in some cases because we have very progressive coverage

for children in this state, children may be in different plans than their parents. So, mitigating that churn and trying to unite families on meaningful coverage with access to the same provider networks and, again, trying to engage consumers in a meaningful way to keep them attached to coverage is very important, and we have tried to approach the discussion with that at the forefront.

Finally, and maybe most importantly, on the entire Health Reform and Implementation of Affordable Care Act, as the Health Care Authority sees it anyway, we want to do reform the Washington way, which means at times where federal regs would perhaps hamper that, or interpretations of statute may hamper that, we will seek necessary flexibility, whether through waiver or different interpretations of regulations, etc. Next slide.

This is meant to give you a picture of what this new coverage continuum will look like in Washington State. At the top, you will see the foundation. It's the new expanded Medicaid program, which goes up to 138% of the federal poverty level, and that's a functional federal poverty level that builds in a 5% income disregard, because the number you've probably heard in the past is 133%. I just want to offer that caveat, and this is for adults. You will see right beneath that, that our children's coverage program, CHIP, more broadly known as Apple Health for Kids, go up to 300% of the federal poverty level. To give you a sense, though, of the Medicaid expansion for a single adult, that's up to $15,000 of annual income is the range of income that we're talking about for the new Medicaid option. Beneath that, you will see premium tax credits and cost-sharing reductions. This is what that new health benefit exchange will be facilitating for consumers, think of it as premium subsidies, and then for those beneath 250% of the federal poverty level, there are additional reductions to their cost-sharing obligations to make the product more affordable and accessing care more affordable to them.

Finally, beneath that, we want to note that there are some qualified health plans that have no subsidy attached to them for folks above 400% of the federal poverty level where the tax credits run out, and this new exchange marketplace will allow people to navigate through those options making apples-to-apples comparisons and making the right decision for their families. Next slide.

Actually, I should note that 400% of the federal poverty level, since these percentages are often unhelpful, is about $93,000 for a family of four of income, to give you a sense.

The next slide here gives you kind of a bar chart presentation of order of magnitude wise how many lives are impacted by the Medicaid expansion and the new coverage options and the exchange. On the left most bar, you will see the current Medicaid population comprises about 1.2 million Washingtonians at any given moment. This also includes state only medical assistance offering, so it's not just federally-financed Medicaid programs that we're talking about there. To the right of that, you will see that 550,000 or so people today are eligible for Medicaid but not enrolled, a surprising number to some, but remember that the majority of that number are children, children who, because we cover them at a very high rate in this state, are eligible but are instead covered through other private sources of coverage and even post Affordable Care Act, since nothing changes for their coverage options, are likely to remain in those private coverage offerings. It does include some adults and children, however, and there is a portion of this currently eligible population that will come into Medicaid, as a direct result of the Affordable Care Act, all the outreach elements associated, and the fact that eligibility will be so much more streamlined and so much more available to people. So, about 78,000 of that 550,000 currently eligible population are expected to come through the doors as part of the welcome mat population. It's the policy term we use to describe this group of folks.

To the right of that, you will see about 500,000 or so newly eligible people as a result of the Medicaid expansion. This is a very significant number. Of course, not all of these people are uninsured, and not all of them will come into coverage as a result of Medicaid being made available to them. There are, in fact, many uninsured people today that are eligible for Medicaid, but for whatever reason are not enrolled. At the end of a four-year ramp-up period, we expect of the roughly 500,000 newly-eligible Medicaid folks, half of that number to come into Medicaid, so 250,000 or so.

To the right, you have another, and this is really order of magnitude territory here, but another 500,000 or so that are eligible for subsidies.

Now, remember the net of all of this. We are not talking about uninsured folks. So, while in the governor's budget release in her policy brief attached the Medicaid expansion, she asserts that 85% of the currently uninsured population in this state will have access through one of these new coverage mechanisms under the Affordable Care Act. It's very good news for the state on both a people front and a fiscal front. Next slide.

There are some costs of not expanding Medicaid that fit into the upcoming policy and budget discussion. The first is perhaps the most obvious, consumers. Consumers would not have the lowest income consumers potentially impacted by the Affordable Care Act would not have affordable coverage offerings below 100% of the federal poverty level. This would be a new donut hole, if you will, but in this case involving full medical coverage for the population. To the right of that, you will see providers are also impacted. Hospitals forsee a 50% reduction in disproportionate share of hospital payments over the course of the next 6 years, as a result of the ACA. This was one of the pay-fors that helped pay for the coverage expansion. Whether or not a state does the Medicaid expansion, these reductions will occur, and of course, the Medicaid expansion was intended to, in large part, offset these reductions.

You will see that large employers also face an impact if you don't do the Medicaid expansion. They face a broader group of folks that they will be responsible for providing coverage for, because it will drop the [inaudible] threshold to the poverty line at 100%. So, an entire new segment of their workforce… the employer will be exposed to a potential mandate penalty if that person ends up seeking coverage in the exchange on account of the employer's offer not being affordable.

Finally, the exchange, and more broadly the administrative impacts of having a major gap in coverage. If there is this major gap in coverage, it makes continuum of coverage an impossibility and people fall through the gaps but also trying to do pass-offs and hand-offs and all of this becomes incredibly complex, if not impossible. Next slide.

I want to show this picture to you, because the opportunity to streamline programs is very real. On the left side, you will see some of the current Medicaid eligibility pathways listed. In many cases,

with the Medicaid expansion these pathways become duplicative, which means the opportunity in 2014 is to have a much more simple eligibility framework. It also means that some of these existing programs will be discontinued. Some that may be most well known to the folks in this room are the basic health plan, which is currently financed through a waiver, 50% federal financing. That population, you heard me reference the refinancing elements of this operation. That population rolls over mostly to 100% federally financing in 2014. One of the big ways the Medicaid expansion nets savings to the state. So, there has been a long discussion with a wide variety of stakeholders on these programs, and you will see some decisions reflected in the governor's budget around these programs and what happens to them in 2014. Next slide.

I'll conclude with this. There is more information available for folks interested in following our path on Affordable Care Act implementation, there is a list serve. We keep people informed of both webinars and in-person stakeholder opportunities, as well as materials, new materials that are constantly being created. We also have a main Medicaid expansion website with some other resources available to you and, of course, an e-mail address for folks if they want a speaker from the Health Care Authority to come engage them on these topics, perhaps a more lengthy presentation at more detail, we're available to you for that. I want to make that offer to anyone in the room. I'll conclude there, because I'm sure I've left, and I've had to by virtue of our time, several gaps in this, and I would await anyone's questions.

Barak Gaster: Thank you, very much Nathan. That was excellent. Questions for Nathan?

Deborah Wiser: This is Deb Wiser. Will this presentation be available to us on the website?

Nathan Johnson: We can definitely make it available, and I would say, too, on the websites you see listed up there, we have a resources page, which has a much lengthier version of this same presentation, which also might be helpful to you. I'm going to go ahead and pass off to Chuck Agte to give us a brief update, if this is the time for that, Duane, on the state plan amendment and where we stand on that for the formulary.

Chuck Agte: This is Chuck Agte, and we have been in the process of putting together our response to CMS's formal request for additional information on our state plan amendment regarding the formulary, and we did complete and submit that last week, possibly the week before. I think it was last week, though. We have submitted our response to CMS. We will be making that response publicly available, hopefully in the next couple of weeks. It might be in the first week of January or so. We intend to make that available on our website so that we are transparent in regard to what CMS questions for us were and how we did respond to those. So, you should be seeing that appear soon, and we'll get the information out on when that is available on our website, and at this point, based on the timing of our response, I am not expecting that we will be hearing back from CMS this month, because like anybody else, I'm guessing they have a lot of people out of the office during late December. So, CMS technically has 90 days to either request more additional information or give us a response in regard to whether our state plan amendment is approved, so that process can take 90 days. It generally is not expected to take that full 90 days, so we could hear a response anytime between now and 90 days from now, and as previously published by the agency, at the point at which we do have approval of our state plan amendment for the formulary, we will be proceeding with the implementation of our first classes we've reviewed so far the first of the month following our approval by CMS. So, that's where we stand at this point in the process with approval and we will get information out, as soon as we do hear one way or the other on approval, and we will do provider notifications to remind people that the formulary is being implemented once we do receive that approval. Any questions on how we're proceeding with the state plan amendment at the moment?

Barak Gaster: So, this is Barak Gaster. I have a quick question that may be best to you, Chuck, or to you, Nathan, that part of this process that's always been a little bit fuzzy for me is the size of the population in Washington, which is Medicaid fee for service versus that which is Medicaid managed care, and whether we predict that the Medicaid expansion will change that mix or keep it about the same?

Nathan Johnson: That's a great question. I'll take the first shot and pass it to others if they want to fill in some cracks. I think, as the folks are familiar with around the table, as of November 1st, we completed the transition of

Medicaid only SSI clients to differentiate them from dual-eligibles to managed care. There were about 100,000 on the fee-for-service caseload during the six-month transition period that moved to managed care. So, who's left in fee-for-service is a great question. There are several major categories of folks, some of whom have exemptions from managed care, from mandatory managed care in those counties where it is appropriate, and others who just have never been included in the managed care population previous. The first and notable exemption from managed care, I guess you would say, is the dual-eligible population. They receive the bulk of their medical care, as well as their prescription drugs, through the Medicare program. There are tribal members. Tribal members are exempt from managed care, and many of them in our state exempt themselves from managed care and received Medicare services through the fee-for-service program. In addition, there are clients that have third-party liability. In other words, there is another payer that HCA has found that is responsible for a portion of their healthcare costs, and they remain in the fee-for-service program. There are also a limited group of folks who have medical exemptions. Foster children are voluntary managed care, and the vast majority of them are in fee-for-service. We also have some of our noncitizen children in the CHP program, exclusively served through the CHP program. All told, if you add them all up, all of the populations and several I've left off who are a little smaller, there is roughly about 400,000 or so beneficiaries on the fee-for-service program. I think the important thing to note, however, is a big portion of that, at least in terms of the expenditures, are among dual-eligibles for whom, as it relates to Medicaid, a big portion of those expenditures are related to long-term care and other waivered service, in-home waivered services, and the like. In the new world with the Medicaid expansion, the vast majority of those newly-eligible adult clients, as well as the welcome mat individuals who are currently eligible, will be served by managed care plans. That is to the extent they live in mandatory managed care counties, and I should explain that when I say mandatory managed care counties, what I'm referring to is enrollees are required to have plan selection available to them. So, in counties where only one plan is able to acquire an adequate network, there is no mandatory enrollment in managed care. Many cases of the vast majority of those enrollees are served in fee-for-service in those counties. That is less and less the case today with the emergence of three new plans through the recent procurement we

have, and I can only think of one or two counties at this moment that are voluntary managed care counties, and they tend to very rural, very low population counties. I hope that's responsive to your question, and we can provide more detail too, in writing, to the extent there is further interest in understanding some of the granular level detail on which populations remain in fee-for-service.

Chuck Agte: This is Chuck Agte. Nathan, because you didn't touch directly on it and I get these questions pretty regularly, so I know there's interest out there, you did touch on the 400,000 figure, a good chunk of that being dual-eligible of specific interest to the pharmacy industry and the pharmacy community because we don't, you know, once they have part D, we're not really involved in their benefits. What portion of that 400,000 is not dual-eligibles?

Nathan Johnson: Great question. It's about 250,000, or a little more. It's bad when I start using numbers, especially when they're not on slides, but it's in that range, and it also includes, I should add people like our family planning programs where it's a limited benefit that's being provided. So, those enrollees are served through the fee-for-service program but for a very limited family planning only benefit, and there's about 50,000 of those, and the other notable thing I left out is at any point in time when someone emerges to the Medicaid program, goes through the eligibility process, their enrollment in managed care is never immediate. In some cases, it takes up to six weeks for them to be enrolled, so there is also the churned effect. So, at any point in time, there is a group of folks that are just awaiting managed care enrollment on the caseload. It's not a huge number, but there is a fair amount, since Medicaid has quite a bit of churn today.

Duane Thurman: This is Duane Thurman. I just wanted to clarify, too, that we're going into a legislative session starting January 14th with a new governor. What Nathan was referring to was the governor's budget, the current governor, governor Gregoire's budget that she released yesterday. She is required to do that, and the first thing that will happen is the new governor will write another budget, and the senate will write a budget, and so we intend to continue our current policies until the policies change. This transition involves the appointment, usually, of all new agency directors, cabinet level positions, that may or may not affect the Health Care Authority directly, but the formulary and the Medicaid

expansion, I guarantee you, will be very hot topics in the upcoming legislature. So, we will try to keep you posted on all that, but it's a time of tremendous change, and we'll see where we end up, but at this point, I just want to make it clear that we are following our current policies, but it will be a long… the issue in this budget is pitted education against healthcare, and it's another horrible $900 million, a billion shortfall again. So, it will be an interesting… and then the possibility of this coalition government you've been reading about. So, it will be interesting. We'll keep you posted, but your work will be in highlights.

Nathan Johnson: I should add one thing too, because there is something else notable about this governor's proposed budget. It's the first time in several budget cycles that, at least as the Health Care Authority is concerned, we've seen no significant reductions to benefits or clients served, which is very good news, and that's in large part due to the savings estimated, as a result of the Medicaid expansion and the decision to re-up the hospital safety net assessment program, which has been a success, so far. So, that hopefully adds good perspective, at least, from the Health Care Authority's view that things are looking… on the whole scale of things, relatively up in terms of the next budget cycle for us.

Christopher Smith: This is Christopher Smith. So, I heard you say that the population that is effected by this formulary is about 400,000 individuals?

Nathan Johnson: It's less than that. It gets confusing. It's less than that because dual-eligibles receive a part D benefit. So, they're not impacted by any Medicaid formulary decisions. The rest, to the extent they're full benefit eligibles, so again then you have to exclude the family planning only recipients potentially, depending on later decisions of this body and others who don't receive a full benefit from Medicaid, but if you really want to have a good rough sense order of magnitude number, give it about 200,000 people who are full benefit eligibles on Medicaid who would be impacted in one way or the other by the Medicaid formulary decision.

Christopher Smith: And that number does not change significantly after the expansion?

Nathan Johnson: It will go up to the extent that some of the newly eligible adults and some of the welcome mat populations will be in those exempt categories I named off, but it will be very slight. It will not change the mix, so to speak.

Barak Gaster: So, this is Barak Gaster. Just to then kind of drive the point home then, the formulary that we are developing for the fee-for-service clients is really only an attempt to design a formulary, which is very similar to the formulary that all of the individual Medicaid managed care plans are already applying to the other clients.

Nathan Johnson: That is correct. All five managed care plans have formularies, and the vast majority of our beneficiaries are under one of those formularies.

Barak Gaster: Alright. Any other questions for Nathan or Chuck? Alright. So now, we are going to move on to our next class review, which is going to be benign prostatic hyperplasia medications.

Christopher Smith: This is Christopher Smith. I can fill in some time here talking to Nathan again. Does the state save money by having patients on managed care plans? Is this a savings or is just less of an administrative hassle?

Nathan Johnson: Well, there's a debate about that, of course, and the legislature did, in the last procurement, the legislature booked a significant amount of savings, as a result of the SSI transition to managed care, largely due to the different management techniques and the different rates that were bid by the various plans that came into the Washington State marketplace, but there is a debate in every state about where the true savings are and what the numbers actually are on a longterm basis.

Barak Gaster: Good morning. Is there a speaker on the line?

Raj Gandhi: Good morning. This is Raj from MedImpact.

Barak Gaster: Hi. Good morning. My name is Barak Gaster, and we are here with the Washington State Pharmacy and Therapeutics Committee convened as our Drug Utilization Review Board, and we would love to hear a presentation on drugs for benign prostatic hyperplasia. So, we are ready whenever you are.

Raj Gandhi: Okay, and who would have the slide control?

Leta Evaskus: Hi, this is Leta. I have the slide control. You can just say next slide between them.

Raj Gandhi: Okay, thank you. Just a moment, let me pull up my Slidex.

Barak Gaster: This is Barak Gaster again. It sounds like the mic on your end may be a little bit fuzzy, so if you could try to speak clearly into the microphone, we would appreciate it.

Raj Gandhi: Sure. Let me see what I can do. Admittedly, it's about the same on my end for your mic.

Barak Gaster: Okay, thank you.

Raj Gandhi: Alright, how's that?

Barak Gaster: Okay.

Raj Gandhi: Is that better?

Barak Gaster: Yes.

Raj Gandhi: Okay, great. I'm having a hard… I don't know if it's just a connection. I'm also having a hard time hearing you, but I'm going to go ahead and jump in, and good morning, everyone. My name is Raj Gandhi, and I'm a pharmacist in the capacity of clinical program manager for MedImpact Health Care Systems, and in the first presentation today, we will review benign prostatic hypertrophy, or BPH disease state. Next slide please.

Since 2003, drug approvals included Rapaflo or silodosin for the treatment of the signs and symptoms of benign prostatic hyperplasia, as well as Uroxatral (alfuzosin) for the treatment of signs and symptoms of BPH. Also, newer indications include Cialis in 2001 for BPH and erectile dysfunction with signs and symptoms for BPH, as well as Avodart, or dutasteride, in combination with an alpha-blocker tamsulosin. It was also indicated for treatment of signs and symptoms

of BPH in men with enlarged prostate. The efficacy and safety of Cialis, or tadalafil, in the treatment of BPH will not be discussed in this presentation, and I would like to go ahead and move on to the next slide.

BPH is an enlargement of the prostate that can be associated with lower urinary tract symptoms or LUTS for short. According to the prostate clinic, incidence of symptomatic BPH is actually about 65% in patients 60 years of age and 90% of patients 70 years of age, and a common misnomer is that BPH is a predictor of prostate cancer, but BPH is not a predictor of prostate cancer. They can and tend to present together, again, it is not a predictor. Slide 4, please.

So, let's go ahead and review some of the symptoms of BPH. As you can see, with the image on the right with the prostate positioned to the bladder and lower urinary tract, enlargement can lead to lower urinary tract symptoms. Something to keep in mind is that the progression of BPH is generally slow and unpredictable and more importantly, not all patients experience symptoms of BPH. Many symptoms of BPH stem from obstruction of the urethra and gradual loss of bladder function. This results in incomplete bladder emptying, and it's important to note that the symptoms of BPH vary, but the most common ones involve changes or problems with urination, such as the ones listed on the slide here.

Some of the obstructive urinary symptoms include hesitancy upon the initiation of urination, decreased force or caliber of the urinary stream, aka weak stream, the sensation of incomplete bladder emptying and intermittent through the urinary stream, and there is also a variety of irritative symptoms, and they may include frequent urination, nighttime urination, or incontinence, urgent urination and, in some cases in urinary retention where the patient is unable to urinate at all.

BPH may, at times, present with hematuria, and it may be complicated by recurrent UTIs, or urinary tract infections or bladder stones. The severity of symptoms may not correlate with the degree of hyperplasia, and lower urinary tract symptoms are not specific for BPH. Next slide, please.

The American Urological Association, AUA, recommends urinalysis, prostate specific antigen level testing, and patient symptom index, as part of their initial evaluation. In the AUA flow chart depicted here, four key options include noninvasive therapy including watchful eating. Surgery is the most invasive therapy and is deemed necessary in the following situations, when there is recurrent or progressive retention that is observed, elevated creatinine secondary to hydronephrosis, postvoid residual, recurrent bleeding refractory to 5X-reductase inhibitors and recurrent UTIs or the presence of bladder stones. [inaudible] minimally-invasive and surgical therapies have been existence since 1994. Next slide please.

Here is an example of the International Prostate Symptom Score, the IPSS. The AUA symptom index is identical to the seven symptom questions of the IPSS on the slide here, and the AUA symptom index or IPSS is – either one of them, they're both questionnaires designed to determine the seriousness of urinary symptoms and are used to help diagnose BPH. The patient will answer some questions related to common symptoms of BPH, how frequently the patient experiences these symptoms, rate them on a scale of 1 to 5, and then essentially just add up the numbers together, and it provides you a score that is used to value the condition. A 0 to 7 means the condition is mild, 8 to 19 is moderate, and 20 to 35 is severe. This is the assessment tool that's most used in efficacy studies for BPH treatment, and the rate of increase in IPSS has been shown to be a prognostic factor in necessitating treatment for BPH. Next slide please.

Alright, so alpha blockers. Within the class, they demonstrate equal efficacy with slight differences in adverse effect and improvement of the AUA symptom index improvement range anywhere from -4 to -6 points; five alpha reductase inhibitors are ineffective in patients who do not have enlarged prostates but are shown to reduce risk of acute urinary retention and BPH-related surgery, and the AUA symptom index improvement is anywhere from 3 points to 4 points improvement.

Finasteride is less effective than alpha blockers on improving LUTS, or lower urinary tract symptoms. Newer dutasteride has been shown to be of similar efficacy as finasteride in terms of symptom score and flow rate improvement, as well as in the prevention of disease

progression while having a comparable safety profile actually, so it's nice. Combination therapy appeared to be more effective in relieving and preventing the progression of symptoms than alpha-blocker monotherapy. Lastly, I would just like to briefly mention phytotherapy. Phytotherapy and other dietary supplements are not recommended but are a treatment option. Next slide please.

So, the goals of BPH treatment are very straightforward. We want to provide patients with relief of lower urinary tract symptoms and prevent clinical progression of the disease, as well as bladder decompensation. This is mainly because progressive BPH can lead to acute urinary retention, chronic renal failure, urinary tract infection, bladder stones, and worsening of symptoms in general. Next slide please.

Nonpharmacological therapy usually involves a technique referred to the watchful waiting, which essentially is where you're incorporating lifestyle modifications, such as decreasing total fluid intake, moderate intake of alcohol and caffeine-containing products, limiting the use of salt and spices, and maintaining timed voiding schedules. Some drugs may also potentiate BPH symptoms, such as sympathomimetics, anticholinergics, and opioids, so you would want to evaluate the risk and benefit of those, as well.

Pharmacologic therapy can fall into three categories of medications, two prescriptions and one OTC. There are five alpha-blockers and two five-alpha reductase inhibitors currently available for the treatment of BPH. Additionally, there are several phytotherapy options. Again, phytotherapy, there are the herbal remedies, which will not be discussed in great detail, but some of the more commonly used herbal remedies include Serenoa repens, saw palmetto berry, and pygeum africanum or red stinkwood.

Surgery is another option in BPH management. Surgery options may provide greater symptom relief than pharmacologic therapies. It is also associated with more serious adverse effects. However, there are newer, minimally-invasive therapies that have been introduced in the last decade for BPH, as listed in this slide. Some absolute indications for surgery include urinary retention, recurrent UTI, hematuria, stones,

renal insufficiency, and these were discussed earlier and referenced by the American Urological Association. Next slide please, slide 10.

So, let's go back to some BPH drug treatment. Alpha-blockers relax [inaudible] muscle at the exit of the bladder, which in turn reduces the resistance to urinary flow. Approximately two-thirds of patients notice an improvement in symptoms. The assignment of drugs was originally introduced to control high blood pressure and so it was designed to be used for several years on a daily basis. If this lowers blood pressure, it can cause dizziness, headache, and tiredness. Five-alpha reductase inhibitors prevent the conversion of testosterone to a more powerful form, dihydrotestosterone, and so gradually the goal is to reduce the size of the prostate over a period of years. They are only really effective in men with large prostates, defined as greater than 40 mL. Possible side effects include reduced libido, impotence, breast tenderness, and enlargement, and a reduced sperm count. Women who are pregnant must avoid exposure to the drug because of possible side effects to the fetus. So, let's move to slide 11.

Roehrborn in 2003 examined three similarly designed agents. These trials were randomized, double blind, and placebo-controlled trials, and they are 12 weeks in duration with 473. Change in IPSS was -6 versus -4.2 points. Peak flow rates were 2.3 versus 1.11 mL. Dizziness was 5.3%, versus 2.9%. Sexual adverse effects were 0.6%. It's not listed here, and I apologize for that, but this is referring to alfuzosin.

Nording, in 2004, studied two doses of alfuzosin, 10 mg and 15 mg, or tamsulosin once daily compared to placebo in a randomized double-blind multicentered trial, another 12 week trial with 625 patients, and the change in IPSS was 6.5 points with alfuzosin 10 mg, 6 points for alfuzosin 15, tamsulosin was a -6.5, and placebo was -4.6. Dizziness for the respective strength in placebo were 6%, 7%, 2%, and 4%, and sexual adverse effects were 3%, 1%, and placebo was 0% as you see on the slide.

Kawabe compared silodosin 4 mg, tamsulosin 0.2 mg, and placebo in a randomized double-blind and placebo-controlled trial. Change in IPSS for silodosin was -8.3, tamsulosin -6.8, and placebo -5.3. Change in Q-max respective was 3.31, 3.98, 2.21, and adverse events,

specifically dizziness, was about 88.6%, 82.3%, 71.6%, and sexual effects include retrograde ejaculation silodosin 22.3% and tamsulosin 1.6%. Next slide please.

The 2003 McConnell evaluated the effects of monotherapy of doxazosin or finasteride versus combination therapy in 3,407 men with BPH and followed up in four and one half years or so, and the change in the AUA symptom index for placebo was -4 points, doxazosin -6, finasteride -5, and combination -7.

Risk reduction for clinical progression was nearly doubled in the combination therapy group versus monotherapy groups, doxazosin 39%, finasteride 34%, and combination was 66%. In the CombAT trial, [inaudible] assessed two-year results with an ongoing four-year study on 4,844 men with moderate to severe BPH symptoms. So, this is an IPSS score greater or equal to 12, and the prostate volume is greater or equal to 30 mL to compare the effect of tamsulosin 0.4 mg to dutasteride 0.5 mg or both, and the change in IPSS for dutasteride is 4.9, tamsulosin 4.3, and combination 6.2. Next slide please.

So, as you have collected already, adverse effects commonly seen in alpha-blockers include dizziness, headache, asthenia, postural hypotension, rhinitis, and sexual dysfunction in 5 to 9% of the patient population as a whole experiencing these side effects. The most common adverse effects seen with alfuzosin was dizziness, about 5%. Syncope, hypotension, and sexual dysfunction were essentially rare. The most common adverse effects seen in silodosin was abnormal retrograde ejaculation, 22% versus 2% with tamsulosin and 0% with placebo. Both tamsulosin and silodosin have been associated with intraoperative floppy iris syndrome, or IFIS. Dutasteride and finasteride have been associated with decreased libido, erectile dysfunction, and inhibition of developing fetus. Next slide.

In conclusion, literature does not suggest superiority in terms of efficacy or effectiveness amongst alpha-blockers. Newer alpha-blocking agents, alfuzosin and silodosin, have minimal advantages. Alfuzosin may have less sexual side effects. Terazosin and non-selective alpha blockers have more side effects, mainly related to hypotension. Alfuzosin may have fewer sexual adverse effects than

tamsulosin and less syncope than terazosin or doxazosin, and although more comparative trials are needed.

Direct comparison of dutasteride with finasteride are lacking. As mentioned, more studies are needed to evaluate superiority, and there is no evidence that dutasteride offers any advantage over finasteride. Five-alpha reductase inhibitors are slow to relieve BPH than alpha-blockers but have been shown to reduce the risk of acute urinary retention and surgical intervention.

Finally, combination therapy may relieve BPH symptoms more quickly than monotherapy for patients with enlarged prostate volume and double the risk reduction of clinical progression. Questions?

Barak Gaster: Thank you very much. Are there any questions for this speaker? Alright, it looks like there are no questions, and so I think that we can let you go, and thank you very much for the presentation this morning.

Raj Gandhi: Oh, thank you for having me, and I will hear back from you later. Have a nice day, Barak.

Barak Gaster: Thank you. Alright, this is Barak Gaster, and now I would turn our attention to the very helpful claims data that is provided for us. At least mine has a little blue sticky on it, and then I have a very helpful list of the current Medicaid status and restrictions on the BPH drugs in terms of which ones are covered and which ones currently require prior authorization. That was near the beginning of my folder.

Susan Rowe: So, right after the agenda?

Barak Gaster: Right after the agenda, thank you. So, if we could look as a committee together at these two lists, and I guess the first question that comes to my mind, which I am guessing the answer is we don't know, is looking at the claims data for finasteride and trying to guess whether… what percentage of those claims were actually combination therapy with an alpha-blocker versus monotherapy, and my guess is that we don't know that.

Donna Sullivan: This is Donna Sullivan. That is correct.

Barak Gaster: Yeah.

Susan Rowe: This is Susan Rowe, and I have sort of a similar question. I'm looking at the large number of our patients that are taking prazosin and it occurs to me that it could be for blood pressure, but not likely, and it could be for BPH, but it also could be for PTSD, nightmares. So, I am wondering what we know about this patient population.

Donna Sullivan: So, this is Donna Sullivan, again. So, that's a good question. We did not limit this to clients that had BPH. So, whatever decision you make here, formulary wise for BPH, is indication specific. So, if there was a PTSD treatment, and we could set up an authorization to allow those to go through if that was the case.

Chuck Agte: And yes, we do allow prazosin for PTSD. This is Chuck Age. So, that is a good point. The utilization you see there for prazosin would be all utilization. These are not broken out by the diagnosis and so how we would implement any decision related to BPH is that that formulary decision would be specific to the diagnosis of BPH and any use of these products whether it's prazosin or others for diagnoses other than BPH, they would not be effected by a formulary decision. So, as we are preparing to deal with the classes that you've made previous decisions on, if you do not voice a specific formulary decision in regard to any particular diagnosis, we are putting mechanisms in place, primarily our expedited authorization codes, to indicate when a product is being used for a diagnosis other than the one that it may be formulary, non-formulary whatever for. So, when you're considering this, you are looking at BPH. Other diagnoses will be handled in such a way that they would still be covered according to whatever criteria we have outside of the formulary and if it's being used for another diagnosis, it won't be impeded by a non-formulary determination in regard to BPH.

Christopher Smith: Chuck, this is Christopher Smith. In terms of the onus on a prescriber, is that diagnostic data apparent due to electronic prescribing at the time of receiving a prescription, or is there a form that's required to specify the diagnosis intended?

Chuck Agte: In regards to formulary decisions, we have kind of a couple – there are a couple of pieces in place there. The primary piece, if it's being used

for a diagnosis that is not part of the formulary decision, is essentially between the pharmacy and the prescriber, and I don't know if it's changed significantly in the last two to three years since we looked at it last, but the last we were looking at it is that, no, pharmacies often do not have diagnosis until or unless they ask because there is a PA requirement of some kind. So, the agency does always actively encourage prescribers to share diagnoses whenever possible, because it does streamline the process. So, in terms of being exempt from a non-formulary status based on diagnosis, if the pharmacy has that information, they have codes available that they can go ahead and indicate what the diagnosis was when they're billing the claim. If they don't have that diagnosis information, they can either seek it from the prescriber and then use an appropriate code if it is for a diagnosis other than, in this case, BPH, and if the pharmacy doesn't know those things and for some reason it falls through the cracks and becomes a submission as a formulary exemption, and they do in fact have another diagnosis, as soon as that came into the PA process, if it missed being exempted at the pharmacy level with an expedited authorization, then as soon as we receive that information, then it would be approved, because the formulary would not apply in that case. So, primarily from a diagnosis basis, that falls into the existing processes that pharmacies use to try and obtain diagnostic information from prescribers, which is often a phone call.

Christopher Smith: This is Christopher Smith again. So, I'm interested from the pharmacist on the committee, maybe from Chuck as well. So, how often do you receive that diagnostic data with the prescription? Is that something that you see commonly now electronically, or are we talking about a lot of phone calls?

Mason Bowman: Mason Bowman here. I see it more often in my situation, because I'm in a clinic, and so the doctors and providers are under the understanding that they do. Not always, though, does it happen, but as far as some of the other pharmacists that are here on the board, they may have a different experience.

Christine Klingel: This is Christine Klingel. Yeah, I also work in a clinic situation, so we do have access to EMR. It is a new criteria, I believe, for meaningful use. So, as more prescribers start complying with meaningful use requirements, it will probably be more common where it has to be – a

diagnosis has to be accompanied, but I'm sure in an average retail setting, pharmacists have created ways to get that information, such as querying the patient or querying the prescriber and calling the prescriber's office.

Eric Harvey: This is Eric Harvey. As far as within the Children's Hospital system, we only capture about 40… we capture less than half of the prescriptions that are written by our prescribers, as far as filling in-house. So, the other 50% go out with no diagnosis or anything. As Mason and Christine said, the prescriptions we get internally we can see the electronic medical record, but outside pharmacies don't have access to that information, so we are sending a lot of prescriptions out with no diagnosis information.

Susan Rowe: And this is Susan Rowe, and I would add to what Eric says. I am also in a clinic situation. I… and to my knowledge, we can link our diagnosis with our prescription; however, that does not print on the prescription, and we're not filling them in-house yet. So, if we've had, for example, trying to use tamsulosin to aid in the passing of kidney stones, I have always instructed our residents to put that in the SIG, so that the pharmacy will know, but I don't think that's routinely done.

Chuck Agte: This is Chuck Agte again. Based on the clarifications that were offered, I should clarify that my comments were more in regard to retail pharmacies outside of a clinic setting. They are the majority of the business that's done, and they, in our experience, usually do not have a diagnosis unless they go looking for one.

Donna Sullivan: And this Donna Sullivan. I think if we were to put an expedited authorization for the indications that you don't address today, the pharmacies and the doctors learn after a few phone calls to start writing… they'll start remembering which drugs need an authorization, and they will start writing that on the prescription, I think. So, there's a learning curve initially, but it does come across… they figure it out.

Barak Gaster: This is Barak Gaster. Thank you very much. Other questions?

Man: We always have to address the negative daily cost. It sounds like you can make a lot of money by prescribing some of these drugs. So,

again, it just has to do with coupons or incentives and things. So, we just presume that's a zero, or how do we look at that?

Donna Sullivan: This is Donna Sullivan. So, in the instance of Flomax where it's a -1.37, you'll see that there were only 31 claims, and that's a multisource brand that has a generic available. So, it's subject to the maximal allowable cost, and there's also the federal rebate that we get for that product, which is causing it to be a negative amount. If that drug was formulary, it would cost a lot more, because the pharmacies would actually call and say hey, you underpaid me for this drug, and they would submit an invoice, and it would go up. So, that is kind of an anomaly, I guess, in the data that those claims claims the pharmacy either didn't notice that they got underpaid, or they just chose not to go through the process, but that's what the negative numbers are, is usually a combination of our maximal allowable cost and the federal rebate. So, at times, we are making money, essentially, on the drugs.

Chuck Agte: And this is Chuck Agte. Correct me if I'm wrong, Donna. To my recollection, we did not exclude TPL claims from our data, and that is also a big factor, especially when you're down to like 9 clients, 31 claims. If there is a primary payer and we're only paying a secondary portion, like 20% of a prescription, if we pay anything on a prescription, we're still entitled to full federal rebate. So, that can also skew the numbers in terms of, you know, that may have been two or three prescriptions where we were only paying the $5 copay remaining but still received full federal rebate on the unit. So, once you're looking at small numbers like that, it only takes a few claims where there may have been another primary insurance to skew the numbers towards a negative, as well.

Barak Gaster: Alright, this is Barak Gaster again. Any other questions? Alright, so then let's turn our attention to building a formulary list for this class of drugs. The obvious brand name that is far more expensive that does not have significant clinical advantage looks to be Avodart.

Deborah Wiser: This is Deb Wiser. As a general approach, I would suggest we make sure we have at least one from each subclass, so either finasteride or dutasteride, at least one alpha-blocker that also has an indication for hypertension.

Barak Gaster: This is Barak Gaster. I think that we will, as we have done in the past, lean towards an inclusive approach to the formulary. So, I think we want to minimize the disruption in therapy, and so if there are several drugs in a class that are all similar in cost and similar in efficacy, I think we will want to include them all, but that's a great point. So, I think what we have done in the past is we have decided to remove all drugs for the formulary except. So, let's make a list of those drugs that we will want to include with the specific instructions we have done in the past to exclude branded products if a generic equivalent is available. So, I think we will want to include terazosin, and I think we will want to include tamsulosin, and I think we will want to include prazosin just to avoid diagnosis confusion and administrative hassle to try to figure out what the indication for the drug is.

Susan Rowe: This is Susan Rowe. So, in reviewing… it actually… prazosin is not recommended for BPH. So, I would like to make it easy for those who are on it to continue, but I just wonder, again, if we're trying to single in on BPH, and it's not shown to be more efficacious or even equally as efficacious. I do appreciate that we don't want to disrupt that number of patients but if it's for BPH, maybe they could be treated better.

Deborah Wiser: This is Deb Wiser. Generally, we haven't included medicines that aren't FDA approved for that purpose, either. This one fits in that category.

Chuck Agte: This is Chuck Agte. To clarify on that issue, by the rules under which we're allowed to have a formulary under Medicaid, we must consider both FDA labeled indications and indications that are supported for use in the compendia, which are AHFS and DrugDex. So, I'm, not having looked at the entry myself, and not being the clinical one, I don't know the level of support in DrugDex that it has for that diagnosis. As you say, from the information you're looking at today, you… the board is free to decide whether or not they believe it is an effective treatment and should remain on the formulary or not, but we do have to consider its indication because of its appearance in the compendia.

Donna Sullivan: This is Donna Sullivan. Nicole did her review of the class, and it is supported in the compendia as effective. So, it's up to your discretion to include it or not include it based on that information.

Susan Rowe: This is Susan Rowe, and I will clarify it was not compendia, it was guidelines—professional guidelines that did not recommend its use.

Chuck Agte: This is Chuck Agte again. To throw out there, when we have included something, because it is considered supported as effective in the compendia, that's not necessarily a comparative efficacy in any way. It just means that there is enough evidence out there to show that it at least works for some people some of the time, essentially. So, it's inclusion as supported as being effective in the compendia does not necessarily mean it is more or less equally effective in comparison to the other drugs. It just means there is enough evidence out there to support that it can be used for that indication.

Barak Gaster: This is Barak Gaster. My inclination to at least start out by discussing prazosin as included in the formulary was the observation that on the claims data that we have, prazosin is double the number of clients of any other drug that is compiled on this list. So, my concern was that leaving it off would generate a tremendous number of phone calls when a diagnosis is not present on a prescription to try to clarify what the indication is and that it may be that whatever small improvement in the care of the patient that we might be able to achieve by leaving it off of the formulary would be outweighed by the number of phone calls, administrative time spent, and potential disruption of care that would result by leaving it off of the formulary.

Deborah Wiser: This is Deb Wiser. I agree.

Christopher Smith: Christopher Smith, I do as well. As much as we would like to help guide prescribers, I think that's not really our role in terms of recommending one product over another if we see greater efficacy. I think we do have to make it available, nonetheless, so that they can choose and hopefully choose the right product.

So, Barak, just to finish on your list of alpha-blockers there, doxazosin is a drug that's been around a long time, like terazosin, and I'm

wondering if the committee feels that should also be included in our list of available choices?

Susan Rowe: This is Susan Rowe. I agree.

Mason Bowman: This is Mason Bowman. I think this list that we've got so far initially is sufficient.

Barak Gaster: This is Barak Gaster. So, we've got terazosin, tamsulosin, prazosin, doxazosin, and then we get to the tricky question of finasteride, which is currently slightly more expensive than the alpha-blockers and it gets back to my question at the very beginning, which was what percentage of these patients are using finasteride as a monotherapy, as opposed to a combination therapy? Because I think there is certainly, as we've seen in the data, a role for combination therapy in many patients who are not achieving adequate symptom improvement on an alpha-blocker that you would add finasteride to that alpha-blocker, and so I think at the very least we would want to include finasteride in the formulary in the guise of combination therapy.

Its cost is not terribly much more than an alpha-blocker, such that I guess I would sort of turn to Chuck Agte to help us to understand if there was a requirement for finasteride that this was combination therapy or that someone had not been able to tolerate an alpha-blocker for covering finasteride versus just having finasteride on the formulary, because its cost is not that much more.

Chuck Agte: We have a couple of options technically. If the board decided, for example, that you wanted to make it available as a combination therapy but non-formulary as an individual agent, something like that, we could either tailor an expedited authorization that specifically details the conditions under which you would want to see it available for use, or if those conditions were conducive to doing through an automated step therapy, we also have the ability for the system to look at the time it's processing a claim and see what other medications the client either is currently on or has tried in the past. So, we have a couple of options, and we can adapt ourselves to whichever way the board goes in terms of a recommendation. So, if you let us know how you want it to be available, we can ensure that it is.

Christine Klingel: This is Christine Klingel. I would argue just to include it by itself or in combination. I mean, obviously for the reasons you stated, Barak, that there are patients who cannot tolerate alpha-blockers. We've seen data that's indicated by itself, it's indicated in combination. I would move to just include it by itself.

Susan Rowe: This is Susan Rowe. I completely agree.

Donna Sullivan: This is Donna Sullivan. I think if you look at the staff time, I mean the medication is expensive. If it takes me or Nicole 15 to 20 minutes to review this, that's $50 or $60 of time from the time it meets all the staff, touches all the staff, to pay for a drug that's going to cost like $5.

Michael Johnson: This is Michael Johnson. I agree. I think for the reasons that Barak mentioned, it's common enough that we use it. We use it in combination for people that are failing at alpha-blocker and sometimes they are having side effects. So, finasteride is the next choice. So, I think this list is comprehensive.

Barak Gaster: This is Barak Gaster. So, we've got terazosin, tamsulosin, prazosin, doxazosin, finasteride, and so we have five drugs that we have consensus should be on the formulary and so we are deciding to leave alfuzosin off, a very tiny number of clients. It looks like it is available, as a cheap generic. No clear clinical advantage. Anybody have a strong feeling about including it or not including it?

Christopher Smith: This is Christopher Smith bringing up Donna's point. If it's… if we don't have a reason to exclude it, it certainly is easier from a recordkeeping perspective, administrative perspective, I think, to have it included on the formulary. It's equivalent, so we're not concerned about it not measuring up, even though it doesn't offer any specific advantages, I think it may be more hassle, I guess is what I'm saying, more of a challenge to exclude it than to just include it.

Donna Sullivan: This is Donna Sullivan. If you go back to the tab that shows the restrictions, we currently don't have any restrictions on the generic formulation of that medication, and there's still very low utilization. So, I don't think that would change much, the mix of utilization would change much based on including it or excluding it.

Deborah Wiser: This is Deb Wiser. I agree that the administrative burden would cost more than leaving it on the formulary.

Barak Gaster: Alright. This is Barak Gaster. So, we have arrived at six drugs for the formulary. So, I think we are ready to make a motion. I will go ahead and read this. This is Barak Gaster. Afer reviewing the clinical information for the drugs within the benign prostatic hyperplasia class indicated for the treatment of the medically-accepted condition, BPH, I move that no single brand or generic drug product in this class has a significant clinically meaningful therapeutic advantage in terms of safety, efficacy, or clinical outcome for the treatment of BPH for any subpopulation. The branded products within the class do not have a significantly-meaningful clinical advantage over their generic equivalents and are excluded from the formulary. In light of their clinical equivalents and after review of the average cost and drug utilization data of the medications in this class, all drugs, except terazosin, tamsulosin, prazosin, doxazosin, alfuzosin, and finasteride shall be removed from the formulary in favor of less costly alternatives.

Christopher Smith: Christopher Smith. I second.

Barak Gaster: All in favor, say "aye".

Group: "Aye".

Barak Gaster: All opposed same sign. So, that motion passes.

Eric Harvey: This is Eric Harvey. I had one question, and it's just regarding the column that says the drugs reviewed. There are a couple of drugs that were included in the review, the presentation we heard, that aren't listed there, and I was just wondering if that list needs to be complete or not. We're missing prazosin.

Donna Sullivan: This is Donna Sullivan. We can update that list.

Barak Gaster: This is Barak Gaster. Susan has just reminded me that I should speak for the record that there were no stakeholders who signed up to give comment for this drug class. So, I think we are complete with that

drug class. We are going to take a 15-minute break, and we are going to re-convene at 10:35.

Donna Sullivan: Excuse me, Barak.

Barak Gaster: Yeah, go ahead.

Donna Sullivan: I don't think we have MedImpact scheduled to be here until 10:45. We'll see if we can get them a few minutes early.

Barak Gaster: Okay, great. Alright, so we'll try to convene at 10:35 if we can. Otherwise, we may not have a speaker until 10:45. Thank you.

Alright, so I think we are ready to go. This is Barak Gaster, and we are now re-convening and we'll turn our attention to the ophthalmic prostaglandin drug class, and we have Lisa Cashman on the line who will give us a presentation on this drug class. Take it away, Lisa, and thank you very much.

Lisa Cashman: Sure, thank you. Thank you for having me. This presentation will review the ophthalmic prostaglandins. Slide 2.

First, I want to say, can you – can everyone hear me okay?

Barak Gaster: Yes, very well, thank you.

Lisa Cashman: Okay, great. Slide 2, the ophthalmic prostaglandins are indicated for the treatment of glaucoma and bimatoprost, which is marketed as Latisse, and is indicated for eyelash growth. For the purposes of this presentation, we will focus on the use of ophthalmic prostaglandins in the treatment of glaucoma. There are currently four agents available, and latanoprost is the only product that is generic. These drugs are dosed once daily, usually in the evening. Slide 3.

Ophthalmic prostaglandins lower intraocular pressure by decreasing the outflow of fluid to the area of the eye called the trabecular meshwork. You can see from the diagram how the fluid flows from the interior area of the eye to the anterior chamber and then out. Next slide, slide 4.

Glaucoma is estimated to affect over two million Americans and accounts for 9 to 12% of all cases of blindness in the United States. An increase in intraocular pressure, which I will refer to from here on out as IOP, often results in optic nerve damage, and the treatment goal of glaucoma is to lower the IOP. Currently, there is nothing else that can be done other than surgery. Typically, the IOP ranges from 12 to 21 mmHg and is abnormally high when it's greater than 21. There is no threshold for IOP for the initiation of open-angled glaucoma treatment. There are patients with IOP of 22 to 24 who have thicker cornea and healthy optic nerve by field testing or imaging that don't require treatment and alternatively, there are patients with IOP of about 18 who may have cupping and field loss and then they would be considered a candidate for treatment. Most clinicians would initiate treatment for a patient who has two separate instances of IOP greater than 25 while some would do so for IOP greater than 22. So, there's no clear consensus regarding what the threshold for IOP is. So, it's truly patient and physician dependent.

Open-angled glaucoma requires pharmacotherapy with an anti-glaucoma agent that works either by decreasing of production or increasing the outflow of aqueous humor. In closed-angle glaucoma, medications may be used during the initial treatment, but these patients usually require surgery. Topical medications work either by increasing the aqueous outflow, and those are the prostaglandins, as we stated. Also, the alpha adrenergic agents, cholinergic agonists, or by decreasing the aqueous production, which alpha adrenergic agonists also do along with beta blockers and carbonic anhydrase inhibitors, and prostaglandins are considered to be in the first line of treatment for glaucoma. Next slide, slide 5.

This slide shows the FDA approvals over time, since December of 2008. I would like to focus in on the latest drug that was FDA approved this year in February, and that is tafluprost, or Zioptan. It was approved for open-angle glaucoma and ocular hypertension, and it is the first and only preservative-free prostaglandin analog. However, as you can see in the little picture on the right, it comes in these little packets and does require refrigeration and care and handling. The little packets are for single use, so once you use them, you have to throw them away in order to minimize the risk of infection. So, there

is a little bit more handling required with this product. Okay, next slide, slide 6.

We are going to move on to review the clinical efficacy data with these agents. Ophthalmic prostaglandins, overall, typically lower intraocular pressure by 25 to 30% and this effect is relatively constant throughout the day and night, so it's a pretty constant lowering. It's not that the intraocular pressure lowers significantly when the drug is given and then sort of goes up at the end. To provide a summary of the efficacy data, we'll look at three major meta analysis that were performed. It evaluated randomized controlled trials of bimatoprost, latanoprost, and travoprost, and they were used for open-angle glaucoma or ocular hypertension in all of these studies.

In the first one there by Van der Valk, et al., they reported on 27 trials that looked at monotherapy of various agents. They found that the prostaglandin analogs, the bimatoprost, latanoprost, travoprost, and timolol were the most effective. They evaluated quite a few products, some of which are not on the market anymore, so I did not put those in. They showed a reduction in peak IOP between 27 to 33% of all these agents and a reduction in the trough IOP, again between 26 and 31%. No statistical analysis was provided. Next slide, slide 7.

Now, we are going to look at the last few meta analysis, the first by Denis reported on nine trials, and they found that bimatoprost and travoprost decreased intraocular pressure moreso than latanoprost, but this difference was significant for travoprost only. In the next meta analysis by Li, et al, they reported on 12 trials and to note, six of those trials were also included in the meta analysis that was performed by Denis. They found that travoprost decreased intraocular pressure to a greater extent than timolol but was not statistically different than bimatoprost or latanoprost. They found that travoprost caused significantly more ocular hyperemia and eyelash changes than timolol or latanoprost but was equivalent to bimatoprost for these changes. Next slide, 8.

Zioptan, we discussed, is the newest agent to market and therefore was not included in any of these meta analysis studies. In the [inaudible] clinical trials showing efficacy, it was given once daily for up to 24 months in patients with open-angle glaucoma or ocular hypertension,

and patients had a baseline ocular pressure of 23 to 26 mmHg. In these patients the intraocular pressure was lowered by 6 to 8 at three months and by 5 to 8 mmHg at six months. This information is in the package insert.

This agent was also studied in a longterm dosing study, which was a free trial primarily evaluating its safety in prolonged use. In that study, the range of intraocular pressure reduction observed during the entire 52-week duration ranged from 4.9 to 5.7 mmHg, thus findings exerted as extraocular pressure, lowering its effect in a stable manner during prolonged use. It was also studied in patients with normal tension glaucoma, and this is the most current type of glaucoma found in Japan, and this drug was actually first released in Japan. This study is unpublished, but they found that the intraocular pressure in these patients were reduced by 4 mmHg, which was significantly greater than placebo. Next slide, slide 9.

Now, we're going to get into the comparative trials. The first we're look at is tafluprost versus latanoprost, which was a non-inferiority trial. While they compared these two agents, it was not powered to show that one was better than the other. All they can show was non-inferiority. So, they took a look at the magnitude of the IOP reduction, and the tafluprost and latanoprost treatment groups were similar and thus supported the non-inferiority of these two agents, and the percentage of patients showing reduction of 20% or more of intraocular pressure was 80.4% in the tafluprost treatment group versus 70.6% in the latanoprost treatment group, and the incidence of adverse reactions did not need to [inaudible] between these two treatment groups. Common adverse reaction was conjunctival hyperemia, which was higher in the tafluprost group than the latanoprost group, but the difference was not deemed to be significant. The results there were another non-inferiority study [inaudible] tafluprost versus latanoprost, and this was a 24-month study, and they also demonstrated non-inferiority. Next slide, slide 10.

We are looking at bimatoprost versus travoprost, and in the trial performed by Cantor, bimatoprost significantly lowered the intraocular pressure versus travoprost at certain time points but not all time points. They found that both products significantly lowered intraocular pressure compared to baseline at all time points over placebo, and

64.5% of patients taking bimatoprost had an IOP reduction of less than or equal to 25% versus almost 40% of the travoprost patients. There was no significant difference in side effect incidence between these two groups.

The next trial was done in African-Americans, and in this trial they found no significant difference in the mean IOP lowering between these two groups. Both bimatoprost and travoprost showed significant IOP lowering compared to baseline and no significant difference in the number of patients achieving a 20, 25, 30, or 40% reduction in IOP between the groups. There was no difference in side effect incidence between these groups.

The next we look at is latanoprost timolol, and this was a combination product given together versus travoprost, and they showed no significant difference in IOP lowering effect between these treatment groups at any of the time points, and the average reduction in IOP was 7 mmHg with travoprost and 6.8 mmHg with latanoprost and timolol product. There was no significant difference in side effects between these two treatment groups; 9.3% of travoprost and 1.8% of the fixed combo therapy patients reported ocular hyperemia, while 5.6% of the travoprost and 1.8% of combination therapy reported foreign body sensation. So, there were no significant differences in side effects between the two treatment groups.

So, if we look at the clinical safety, and this slide just goes over the adverse effects with all these agents, they all share the same adverse effects. Latanoprost may be less likely to cause hyperemia, which is redness of the eyes, which I'm sure you all know, compared to some of the other products, but the other effects associated with all of them, in addition to the conjunctival hyperemia is darkening of the iris, increase in length and number of eyelashes, increase in the periorbital skin pigmentation, and some iris pigmentation changes, and those iris pigmentation changes are permanent. Some of the local adverse events are local irritation, itching, dryness, and blurred vision, uveitis, or cystoid macular edema. Systemic effects are rare with these agents. Next slide, slide 13.

In conclusion, most ophthalmic prostaglandins are the most commonly used drug class for the treatment of glaucoma, and they are considered

basically to be equally efficacious lowering intraocular pressure by 25 to 30%. Bimatoprost may decrease intraocular pressure slightly more than latanoprost and travoprost. However, the clinical significance of this difference is not clear. Side effects, such as hyperemia, ocular pruritus, and eyelash growth are reported to occur more often with bimatoprost. With that, next slide. I would like to stop and ask if there are any questions.

Barak Gaster: Thank you very much, Lisa. Are there any questions?

Susan Rowe: This is Susan Rowe, and I wondered if in the reformulation of the travoprost if there was reduction in side effects noted with the elimination of the preservative?

Lisa Cashman: In the trials that they looked at, they showed no significant difference in the side effect and the reformulation, as you can imagine, you know, that was probably the main goal of providing a product that has no preservative in it. The preservatives have been known or were thought to cause a lot of the side effects. I believe all the products now with the preservatives and benzalkonium chloride have been discontinued, which was Travatan. You may recall Travatan used to be a product and now it's Travatan-Z because it doesn't have the benzalkonium chloride in there. It has a different preservative system in there now. But no, they did not specifically… they haven't come out and looked at that.

Susan Rowe: Thank you.

Barak Gaster: Other questions for Lisa?

Christopher Smith: This is Christopher Smith. Can you tell me what you know about the bioequivalence of the generic preparations in this class, as compared to their branded products?

Lisa Cashman: I did some research on that. That came to us, actually, as a drug information question a couple of months ago. So, that was pretty timely. I did some research and there were… this question had come up a while ago. It was in the literature, and the main medical society for ophthalmology came out with a statement that stated that the

generics were equivalent to the brand. That was the gist of it. If you'd like, I can find that and send it to you.

Christopher Smith: I think that would be helpful if that's possible to do today.

Lisa Cashman: Sure. I will send that to you…

Donna Sullivan: Lisa, this is Donna Sullivan. You can e-mail it to me, yes. Thank you.

Lisa Cashman: Yeah, I'll send it to you.

Christopher Smith: Lisa, again, Christopher Smith. So, you… just to clarify, you said that was a national organization representing ophthalmologic physicians?

Lisa Cashman: Yes. You said it a lot better than I did, but yes.

Barak Gaster: This is Barak Gaster, which found the generic formulation to be equally effective as the brand name?

Lisa Cashman: Yes. They found them to be equally effective.

Barak Gaster: Okay, thank you. So, again this is Barak Gaster. I think because much of our decision today is going to hinge on that question, it would be great if we could have that presented to us.

Lisa Cashman: I will look for it, and as soon as I find it, I will e-mail it over to Donna. Donna, I don't know. Do you have access to your e-mail there?

Donna Sullivan: I do, yes.

Lisa Cashman: Okay, okay, great.

Barak Gaster: So, thank you, Lisa. If you could stay on the line. Now, we have one stakeholder who has signed up to present to us, and that is Dr. Agnes Huang from the Washington Academy of Eye Physicians and Surgeons. So, Dr. Huang, thank you for speaking to us. I'll just remind you that you have three minutes to speak for us today.

Agnes Huang: Okay. I am a glaucoma specialist. I train at John Hopkins. I have been in practice for 17 years. Glaucoma is… I do that 100% of my

practice. One of the questions that is coming up today is about the equivalence of generic latanoprost versus Xalatan, and I actually also did a literature search, and there is a big difference in what we call the bioequivalence versus the therapeutic equivalence of the medication. The thing is, if you look at the laws, for eyedrops, you just have to show that you have the same amount of the drug in the bottle and that you administer it the same number of times a day, and it's done in the same way, so eyedrops, and that's it. There have not been any studies that looked at actual therapeutic equivalence whether an eyedrop in this bottle has the same concentration of the medication once it's inside the eye, and this is very different from systemic medications where you take a pill, you draw the blood, and you can measure the concentration. To get the concentration in the eye, you need to go in and withdraw some of the fluid from inside of the eye. This is a little bit more risky for most people, so therefore, this particular study is not being done. So, we have to rely on studies where we look at a drug where you look at the intraocular pressure control, and then you look at the other drug, you may do a crossover study. There was actually one that was done in India in 2007, which looked at Xalatan manufactured by Pfizer and then by their generic, latanoprost manufactured in India. They took 30 patients, they did a crossover study, and they found that there was definitely a 38% decrease in intraocular pressure on the brand of Xalatan versus a 25% decrease in intraocular pressure on the generic. When they did the crossover study, they found that the people who were originally on the generic then had the additional decrease in intraocular pressure compared to, then the people who crossed over into the generic, the intraocular pressure increased to the same level. Now, again, a very small study. More needs to be done. The latanoprost has only been out for a little under two years, and so the American Glaucoma Society, of which I am a member, has been talking about we need to do more studies to look and see whether the actual efficacy of the medications are the same. The problem with eyedrops is, it's not just the medication that's important. It's everything else. It's the excipients. It's the things that buffer the solution. It is the vehicle the solution comes in. It is things that adjust the pH, and those help with the eyedrops absorption into the eye. An example was that there was one of the medications she talked about earlier, Alphagan. It is an eyedrop where it originally came in the 0.2 concentration. A lot of people had allergies and red eyes. The pharmaceutical decreased the concentration to 0.1%, but they did it by

changing the other ingredients, and therefore allowed the medication to come into the eye at the same therapeutic level by decreasing the concentration. So, it just shows that by changing the vehicle that the medication comes in, you can affect how the medication is absorbed into the eye and into what we call the aqueous humor. Just anecdotally…

Barak Gaster: I'll just remind you that you're at the end of your three minutes if you could conclude your remarks.

Agnes Huang: Okay. I just… my feeling is that there's a lot of information that we need to know a little bit more about the equivalence of generic eyedrops. There is a lot of indication that when some of these medications have gone generic, the efficacy has decreased. I think we do need to look a little bit more than just cost. Also, just so you know, with Xalatan itself, the brand of Xalatan, there are about 10% of people who are nonresponders and they did need to go to one of the other medications in that same class to respond to get a decrease in intraocular pressure. So, we need to have more than one choice available. Thank you.

Barak Gaster: Are there any questions for Dr. Huang?

Michael Johnson: I actually have one.

Barak Gaster: Yes.

Michael Johnson: Hi, this is Michael Johnson. Just from a clinical perspective, when you look at people that have elevated intraocular pressures, and you start them on one of these products, when do you expect to see a reduction? In other words, when are you retesting them, and what kind of a response would cause you to look at other alternatives?

Agnes Huang: Generally, what I do with a patient is I bring them in, I give them the drop, and I tell them the intraocular pressure will decrease fairly quickly. However, we are looking at side effects, so most clinicians will bring the patient back in anywhere from two to four weeks and then check the response. As we all know, there are changes going towards a mean, you know. Intraocular pressure varies quite a bit, so you need to do more than one measurement to see how the patient

responds, and so what we're looking for is whether the medication brings a pressure down that stays down and then also they don't have side effects from the eyedrop. That's the biggest problem with compliance is side effects and cost.

Barak Gaster: Great, thank you very much.

Christopher Smith: Just one more question, Dr. Huang. I'm grateful that you took the time to come here today. Could you tell us, do you receive any financial support from pharmaceutical companies?

Agnes Huang: I do not. I am actually a board member of the Washington County of Eye Physicians and Surgeons. I'm a member of the American Glaucoma Society. I also treat 100% glaucoma patients, so I've seen the vast specter of what happens with some of these medications, as they come into play. So, my feeling is I really would like to have choices in order to take care of the patients. I have no problems with generics if they respond to generic and they do very well, wonderful, but there are currently with latanoprost, there were seven, there are now 10 different manufacturers of generic latanoprost, one of them manufactures, in fact, when the drops come in, you actually have to do that… like you do for some of the glues, you know? You have the little poky thing that you have to poke the hole in the cap. So, they put the drop in their eye. So, the drop sizes aren't even the same, whereas with a branded one or some where you know the bottles are the same, you know exactly… they're getting how much of that drop, however many microliters. Some of these other ones coming in, I've had the patients bringing them in, and I'm looking at them and they come in, and it's like they run out of the drops. They're supposed to last, you know, for 30 days, and some of these the drop sizes, you drop them out and they come really big or they come really small. I've had a lot of complaints with some of the generic drugs where the patients run out after three weeks. They can't go medications unless they pay out-of-pocket. The other thing, too, and this doesn't…

Barak Gaster: Thank you, Dr. Huang. I'm going to ask you to conclude your remarks.

Agnes Huang: Thanks.

Barak Gaster: Okay, thank you. Are there other questions for our speaker, Lisa? Great. Thank you very much, Lisa, and were you able to find the guidance statement that you had referred to?

Lisa Cashman: Yes, I found the article, and I sent it to Donna.

Donna Sullivan: This is Donna Sullivan. I'm e-mailing it to Leta right now so she can display it.

Lisa Cashman: Okay, and then just to let you know, Donna, once you get to the article you have to click on the link at the bottom of the page.

Donna Sullivan: Okay.

Lisa Cashman: If you have any problems, just give me a call.

Donna Sullivan: Okay, great. Thank you.

Lisa Cashman: Okay, thank you.

Barak Gaster: Thank you, very much, Lisa.

Lisa Cashman: Sure, thank you.

Barak Gaster: So, let's take a moment to get that guidance statement up on the screen so we can review it. While we're waiting for that…this is Barak Gaster, we can begin by looking at the claims data that has been provided for us for this drug class.

Christopher Smith: This is Christopher Smith. Donna, in the past, we've had some formulary. I know you're occupied, maybe someone else could consider this, but we've had formulary data from some of the commercial insurers. I wonder if we have any formulary exclusions that other major insurance companies have in Washington State?

Donna Sullivan: I can pull up the UMP formulary, but I don't have… I did not prepare the actual insurance… the other managed care plan exclusions. I'm trying to multitask here. I'm going to try to save that study on a thumb drive for Leta. So, Xalatan on Uniform Medical Plan is nonpreferred, so it's tier 3.

Christopher Smith: Christopher Smith. Any other exclusions for the other brand products?

Donna Sullivan: I have to check them one at a time, so hang on. Travatan is tier 2 but it requires step therapy for the generic latanoprost first. Lumigan is the same. It requires the use of latanoprost first.

Christopher Smith: Christopher Smith. So, what you're saying is, for UMP, all new prescriptions for glaucoma patients are for generic latanoprost? Is that what you're saying? That's their formulary choice and you have to go through that before you receive any other options?

Donna Sullivan: Correct, and I'm looking to see what tier they are. The Xalatan is definitely tier 3. I'm checking on the other two, because they did have a preferred drug listed, so. So, the Travatan is preferred, so it's tier 2, but it does require the latanoprost first.

Barak Gaster: This is Barak Gaster. I just want to understand better what it is that we are working on trying to get up here. We were under the impression from the speaker that this was a statement from a national organization, but I'm wondering now if it looks like this is just an article in a magazine with a few experts weighing in.

Donna Sullivan: Yeah, I'm not exactly sure where the statement is.

Barak Gaster: If this is a freelance journalist, I'm a little leery of introducing this data into our consideration.

Donna Sullivan: Okay.

Deborah Wiser: Deb Wiser. In the references listed at the bottom, is there a national organization they are referencing? It looks like there is a list of five references just above where it says Mr. Murphy.

Barak Gaster: Alright, so let's stop pursuing that line, and I guess if we had Lisa on the line still…

Regina Chacon: Do you want me to call her?

Barak Gaster: Yeah, so…

Donna Sullivan: We could… this is Donna Sullivan. We could get her back on the phone if you'd like.

Barak Gaster: Yeah, let's call her just to… because I think we're… we got a little bit mislead by what she said, so it may be good to kind of circle back and ask for, again, to… maybe she sent us the wrong thing or if she misspoke. Let's find out.

Christopher Smith: This is Christopher Smith. While we're waiting, I think the committee can certainly begin our contemplations together. I'm not an ophthalmologist, of course, and I don't prescribe glaucoma medications, but I have colleagues who do, and I talked with them, and the one thing that I heard from them is that there are a lot of interactions, a lot of reactions to the medication, often irritations that are unpredictable, and they said that whatever you do make sure that there is more than one option that is readily available, because they often have to switch. You can't reliably just go on one medicine. The majority of people will need to be switched to another agent. So, it's an anecdote. It's hearsay from a colleague, but I think that's perhaps something that we've been hearing about, as well, from our speaker, is that reactions do occur quite commonly. So, I'm curious if others have formed that impression from their research on the topic?

Mason Bowman: This is Mason Bowman. No, no research particularly the way you were saying, Dr. Smith, but in reference to what was said earlier by Dr. Huang, in the pharmacy that I work at, we do have some of those generics come back frequently because patients say they ran out too quickly. I've had that happen before with the brand, but not as much. It's pretty frequent with the generic product that we use. So, I just wanted to throw that out there.

Lisa Cashman: Hi, this is Lisa.

Barak Gaster: Hi, Lisa. This is Barak Gaster. Thank you so much for coming back to join us. We just want to… we had a follow-up question regarding the article that you sent us, and we wanted to clarify your remark earlier that there was a national organization that had made a statement about the bioequivalence between the generic and branded products in

this drug class. I just want to get followup from you and if you had more information of what exactly you meant by that.

Lisa Cashman: Well, this article… when did I initially send this? It was back in September. Yeah, I looked at it, it's optometric management, and I would need to go back through. It looks to me that they had done quite a lot of analysis and had looked at all the available information and that they had concluded that overall that there was… that it was safe and that it was also equivalent to the brand.

Barak Gaster: Right. This is Barak Gaster. Our question was that it looked to be an article that was written by a freelance journalist consulting with a few experts, but not a statement from a national organization of optometrists or ophthalmologists. Is that right?

Lisa Cashman: Correct, yeah.

Barak Gaster: Okay.

Lisa Cashman: I misspoke on that point. I thought it was from a higher authority. Then when I actually pulled the article back up, it was not.

Barak Gaster: Great. We just wanted to make sure that you hadn't sent us the wrong thing by accident, and again thank you very much for your time.

Lisa Cashman: Sure.

Barak Gaster: Take care.

Lisa Cashman: Thank you.

Barak Gaster: Alright. So, this is Barak Gaster. So, we can now refocus ourselves on the question of what a formulary for this drug class might look like, and Dr. Smith has shared an anecdotal thought about a desire to have more than one medication in this class if somebody doesn't tolerate one, because of an adverse effect. I guess my thought is that the difficulty is then, well, which one do we choose, and I would advocate that we try to stick with one medication that would be the preferred drug that people would try first and that obviously if they're not able to tolerate it, that any of the other drugs in this class could be available

with prior authorization and that we've heard concerns about the quality of generic latanoprost and I think that those are concerns that are well taken and that we would hope that the FDA would respond to the concerns that are raised, but I think that it would be very likely that if we looked at all of the other formularies that are being developed for this drug class, that they all would advise that clinicians begin with the generic, and if there is a failure to respond or an adverse effect from that generic that one of the branded drugs could be requested, but I think looking at the claims data that we were provided, you know, there's a 10 times difference in cost for a drug which we have seen data is equally effective that would lead me to advocate for us having latanoprost to be the preferred drug on our formulary with a mechanism for prior authorization if a clinician had tried latanoprost and found it to either be ineffective or to result in an adverse effect.

Susan Rowe: This is Susan Rowe. I am wondering if we were to go that way, is there anything we can do on the ability for a patient to fill it early if they indeed run out, especially given the difference in price? I feel for the patient's stress level running out of a medication when they've been using… been adherent and using it the way they're supposed to, that they feel like they can't get their medication. So, I wonder if there's a mechanism there?

Chuck Agte: This is Chuck Agte. Currently, the same criteria would apply for this drug, as we do to all drugs in terms of early refill. So, to just let you know where our current policy is, and we would definitely take the board's advice on anything that they may think we need to alter for this particular drug potentially. Currently, we have a 25% allowance in terms of filling a medication early. So, that means that essentially for any drug with a 30-day, prescribed as a 30-day supply, you could actually refill after 22 days. So, we already have a 25% allowance built in. We also have a process, presuming the pharmacy requests authorization, if they actually do hit early refill because they're at 20 days or earlier on a 30-day supply, we do allow an authorization once per six months for an early refill if a drug is lost or stolen. If we get a change in direction on the medication, then that would… the change in direction would also allow for an early refill. So, the way our current policy works essentially, you could get it filled after 22 days. So, a 30-day supply really has to last just a little more than three weeks. In addition to that, it would be our presumption that if a prescriber was

finding that a client was using a bottle that was intended to be a 30-day supply, they're using it appropriately and they're still running out early that the prescriber could adjust directions on that so that they wouldn't be having that problem. So, if a client was consistently using what may be considered a 30-day supply whether it be due to, you know, there could be issues of client training there in terms of how to make sure they control the dosing better, but if it's just a problem with the packaging, the way it's delivered, etc. If a physician found that this particular product lasts 21 days, then they could prescribe accordingly for that volume to be a 21-day supply. So, there are a few ways around that in the process right now, because we have a relatively liberal early refill allowance compared to say private insurers. So, I don't know if the stakeholder spoke earlier whether her experience was in general with insurance carriers period, or with Medicaid, but generally we don't run into that problem, because we have an allowance.

Susan Rowe: Thank you.

Christine Klingel: This is Christine Klingel. I guess I have a couple of thoughts. Looking at the numbers, it is a small proportion of our patients who actually are on these medications, and it looks like the majority of them are on the generic. I'd be curious to know why the ones who are on the brand are on the brand, if they did try and fail, and how that was accomplished. I know we haven't addressed dispense as written rules yet or maybe we have, as far as similar to the preferred drug list where if a prescriber absolutely wanted their particular patient to have the brand, if they could have that power, if we could somehow create that power for this particular class, because it appears there is still a debate or a controversy, as far as whether they are equivalent if they are a generic product, but I don't know how that would work in this type of a situation.

Chuck Agte: So, this is Chuck Agte. At this point in time, there is no automatic bypass or allowance in regard to the formulary for a dispense as written. In general for the process as designed, a prescriber would have to let us know why the generic was not an appropriate option for the client. So, if directed by the board, we could do otherwise, but in general in the way we apply our policies, it is assumed that an FDA equivalent is in fact equivalent and someone's opinion that they don't

believe that or disagree with that is not sufficient in and of itself. So, for example, if the generic for the option in this class and somebody wanted something else, they would have to let us know why the generic was either clinically inappropriate for the client, or have they had an adverse reaction to the product? Clinically inappropriate, when we use that term we're referring to a reason why the client should never take it to begin with, as opposed to they've tried it and had an adverse reaction or they've tried it and had insufficient clinical outcomes from it. So, we could accept direction otherwise, but at this point in time, whatever products are determined to be formulary, we would need to know why that was not an option for that particular patient other than if it's a brand versus a generic issue because we honor FDA equivalency. If it's rated equivalent by the FDA, we consider it equivalent and you need to provide specific information as to why this client had a problem with the generic in that particular case.

Nicole Nguyen: This is Nicole Nguyen. I just wanted to add, I've been trying to check and see if we have, because there is a generic now and a lot of times once the generic is out awhile, a mac is put on the product, so a pharmacist, they try to bill the brand name, they'll get paid for the generic. So, the only way they'd have to ask for prior authorization, and I haven't been seeing requests come to me of them wanting brands and trying to get justification for it. Like there might be some classes, like when some of the atypical antipsychotics I'll get a few requests for those coming through. So, until I can find out if we have a mac on it, I don't know if the reason I'm not getting them is because they're not seeing a big enough problem that they're wanting the brand or they're still getting paid for the brand right now.

Donna Sullivan: This is Donna Sullivan. Christine, I don't know exactly when the generic latanoprost came out, but this data is calendar year 2011. So, I don't know if it was 2007 when that study was published, if that's when the generic was available in the United States or if it came out later, and we're just seeing the substitution rates because of the data period.

This is Donna Sullivan again. I do want to point out that Zioptan is also included in the monograph. It's not on the list of medications, because we do not have any utilization. So, it is still a part of this

class, as well, and I just wanted to make clear that we didn't leave it out of the class, it's just no utilization so it doesn't appear on the utilization spreadsheet.

Christopher Smith: This is Christopher Smith. Christine, you had another question as to how to interpret the current utilization for some of these clients are on the Travatan and whether they got there because they failed the latanoprost. Do we know why that is or is it just a nonrestrictive formulary?

Chuck Agte: This is Chuck Agte. Currently, within the class, with the exception of the Zioptan just mentioned, all of the drugs are currently covered. So, in absence of a formulary decision at this point in time and in absence of having established prior authorization criteria, currently a prescriber could select any of these options other than Zioptan. Zioptan they could select, but it would require prior authorization. So, at this point in time, they could have essentially if they're on one of the other medications, it's because that's what their doctor prescribed. They could have reached that from trying something else first or it could have been used firstline.

Christopher Smith: Christopher Smith. It's interesting with that degree of freedom that they're not running away from the generic, that the clients are on that generic agent. So, that tells us that at least it's trusted by the prescribers and generally well accepted.

Nicole Nguyen: This is Nicole Nguyen. I probably sense this data has been out since I'm seeing requests. I have probably seen, I'm guessing, less than around five or less of the new drug requests so far.

Barak Gaster: This is Barak Gaster. I would just put in another comment that if somebody is put on the generic drug and does not respond and then is switched to a brand name, that the overall harm to that patient is very small. A month or two of higher intraocular pressure is not going to make a clinical difference for that patient, that a month or two of a mild side effect from a generic drug is unlikely to have any significant impact on that patient, and that, as Christine said, it's true that this is not a high number of clients. It's still the ten-fold difference in cost will still add up to make an impact, such that I would still advocate

that we have a single medication on the formulary, which would be the generic latanoprost.

Christopher Smith: This is Christopher Smith, and I agree with that conclusion.

Donna Sullivan: This is Donna Sullivan. So, I just want to ask the board's comment or opinion on if you go to one product, do you feel this is something that people could change from an existing product to the latanoprost, or would you recommend that latanoprost be formulary for new starts? Because as it is now, if the other ones become formulary, then we will be requiring them all to go through the non-formulary justification process, so I just want you to be aware of the process and how it all works.

Deborah Wiser: This is Deb Wiser. My concern is if most of the people that are on the brand name drug now had that prescription by someone who believes it is less efficacious. They will feel they need to bring the patient in to see once they're on the generic they'll need to retest their eyes, which would be an increased cost to the system. It makes me lean towards grandfathering those that are already on it.

Barak Gaster: This is Barak Gaster. I would just point out that the cost of that one time check is likely to be far smaller than the difference in cost between the brand name and the generic name for a year of medication.

Deborah Wiser: This is Deb Wiser. I'm not sure if that's a ten-fold cost. That one number on there is a negative number. When I look it up on the apothecaries for the retail cost, it's about a third, latanoprost is about a third of Xalatan. So, I'm not sure in reality what the numbers are.

Donna Sullivan: Well, I would have to look at our actual mac rate, but I do believe that we have a maximum allowable cost on it, and then you have to remember that this is also net of rebate. So, it's really not comparable at all to what you're seeing out there on the retail market. So, I would have to actually look it up and tell you what the per unit maximal allowable cost is.

Chuck Agte: This is Chuck Agte. We are in fact trying to look up the mac on these products right now, but we're having trouble getting back into the state system right now.

Christopher Smith: Christopher Smith. I would be concerned with asking people to switch to the generic not knowing why they ended up on Travatan in the first place and whether they had already tried it. Indeed, we could have a lag time in asking the prescriber to fill out paperwork, but it's very hard to know what the ideal thing is. It seems to me that may prove to be onerous and unfair to ask everybody to switch to the generic or our single formulary choice.

Chuck Agte: This is Chuck Agte. To provide some insight in terms of process, how any non-formulary decision is implemented, so first as a reminder, the board has the option and should feel free in any drug class review to address and let us know when they believe that grandfathering would be appropriate for the class for whatever clinical reason that you determine. As far as the actual request process, so that you know, even for if say… let's just say tomorrow we're turning on a change to the products that are allowable in this class based on the formulary decision, a client who is on a medication currently the first time that they hit a rejection for non-formulary we have processes in place, and it is a requirement under current Washington Medicaid law that we continue anything a client is currently receiving until they receive official notice that they will not receive it in the future. So, what happens, so if we take the example of a brand versus generic in any class, the brand has become non-formulary, if we don't grandfather, then first we do a lot of communication out to the prescribers to begin with to let them know you're prescribing a medication for this client that is non-formulary, so they have the advanced opportunity to get requests in before the actual change happens. If no change has been made when the request comes in, the client is automatically approved for at least one fill of whatever they've been receiving previously, so clients are not cut off with a gap in therapy there while we go through a PA process. They are approved for a fill of whatever they've received before while the authorization process is initiated. So, there is, in theory, no gap that would… because a prescriber would then have the opportunity to send us the information the client has in fact failed the generic or there are these reasons why the client should not take the generic. So, if there are clinical reasons why it is

inappropriate or would be… actually have negative outcomes for a client to switch medications, they should definitely consider that and let us know when grandfathering is appropriate, because clients just shouldn't change medications. If the concern is that there could be a gap, I hope I've addressed that, because clients do receive continuation of benefit until we've reviewed the request from the physician.

Christopher Smith: This is Christopher Smith. We may have addressed this before, but do these communications to the prescribers include a simple fax-back form with the patient's name and the capacity to check a box highlighting one of the reasons, such as prior side effects or insufficient response without having to go through a stack of charts and find notes and dates and how many other medicines were tried?

Chuck Agte: The process that's been developed for review of non-formulary justifications in our initial communication, no. There isn't something sent to them in the initial communication. In the initial communication they do, though, receive a link to what the process is and where to find the form that they fill out. So, the form would still have to be completed by the physician. The degree of what needs to be supplied along with that would vary depending on the drug and the drug class, but the form basically goes through and addresses the basic criteria of, you know, tell us what drugs that they have tried and what the outcome was, and depending on how that outcome is described, it may or may not need supporting chart documentation for clinical reviewers. In a lot of cases, for the most part, we accept a physician's word for it. If we get the form back and it's a drug class where there is only a single formulary option, they're basically going to have to write down here is the drug that they tried and here is why it didn't work for the client. So, no, it's not really a check box, but it's pretty straightforward to say, for example, the patient tried latanoprost, did not have sufficient reduction in IOP, and that's potentially enough to go ahead and approve another medication in the class. Nicole could comment more specifically on the degree of documentation that we might want around that, but generally, we take a prescriber's word for what they tell us.

Christopher Smith: This is Christopher Smith. Sometimes those forms are daunting. When was the medicine tried? What were the dates of usage? What was the reaction to medicine, and what you're really asking about is

was the generic latanoprost tried, and if your records can substantiate why the patient can't go back to it. That would be really simple, like a two-step process, I think, would be much kinder and more appropriate to facilitate answering that question and deciding who can safely switch back and who really needs to remain on a branded drug.

Chuck Agte: This is Chuck Agte again. For the non-formulary justification process, with feedback from the Washington State Medical Association, that dates and lengths of trial are potentially too onerous to be searching for in client records, we have removed that from the information we're asking for. So, at this point, in regard to any non-formulary drug, we're really just asking, and it's broken out into a couple of questions, but what we're looking for is why can't the client take the formulary drug? And we're not asking for give us specific dates and lengths of trials. We're just asking for a detail of what they have tried and what the outcomes were.

Nicole Nguyen: This is Nicole Nguyen. Usually when I'm looking at requests, I want them to tell me what they've tried. Have they tried the generic and tell me what happened. I feel if they can tell me that they had less efficacy or they had some side effects, that's enough for me that they have evidence. I don't need to have them send, especially if it was 10 years ago on some drug. They might not have those records to give me that, so I don't go over all that. That's important. If they can give me that information, I trust that they're saying it.

Chuck Agte: This is Chuck Agte again. In regard to how onerous the regular PA process that you may experience now is or isn't in some cases, generally when we do want chart notes and we're looking for specific documentation, it's usually in regard to diagnosis for conditions that may be questionable or open to controversy on thresholds of what represents an accurate diagnosis or documentation of symptoms, side effects, that kind of thing. In most cases, if the criteria is really just around tried and failed or intolerant to or clinically inappropriate for a client, that's something that we take the doctor's statement for. So, usually, quite honestly when I hear from my clinical staff, they find receiving charts in a lot of cases more annoying, because often there is a situation where a doctor could have just written a sentence saying, here's the situation, and that would have been complete, and instead we get a document that says see chart notes, and you have 20 pages of

charts to go through to find the relevant sentence that could have been transcribed once. So, we're often not looking for chart notes and in-depth detail, like I said, unless it's a diagnosis that requires some substantiation that the diagnosis is actually what's going on with the patient. When it's merely a matter of what drugs has the patient tried and what were their outcomes, that can just be detailed by a doctor and, again, they sign the form and we take their word for it.

Christopher Smith: This is Christopher Smith. So, does the request for information…

Chuck Agte: I'm sorry, can you repeat that?

Christopher Smith: Does the request for information clarify that for the busy prescriber that all we're looking for is a physician statement and chart notes are not necessarily required? Because I can imagine in glaucoma specialist's office recognizing that 30+ patients all of a sudden have this need for justification, you know, being reassured that an exhaustive chart search is not necessary would go a long way to facilitate in care.

Chuck Agte: Without the document right in front of me, I can't be that detailed, but it is a generic questionnaire in terms of the formulary drugs, in general, so it's been designed to try and address the needs of what we're looking for, and it's essentially broken out into, you know, what is the client's diagnosis? What drugs have been tried and failed? Then there's an opportunity to provide other clinical information. The form does not specifically state that chart notes are optional. The form says that essentially in so many words it says that if you need to… if you feel the need to attach chart notes to document anything then do so. It basically gives the option to use additional supporting information should you decide to attach it. It doesn't say that it is or is not required, because it really… when we're looking forward towards the full spectrum of what might be involved in the formulary over time. Some drugs may require more justification than others, and it is general to the basic points of what are the treatments that have been tried for this client and why are the formulary options not appropriate for them?

Christopher Smith: Christopher Smith. I just suppose what I'm asking is in a situation like this where it's really a question of have you used this one drug, it

seems that using a separate form that streamlines the process would be more efficient for everybody and may not be more onerous to just create a link to this other ophthalmologic glaucoma medication form.

Donna Sullivan: This is Donna Sullivan. We can look into maybe… I mean as we move forward, we can look into having different forms or maybe a custom form or something like an addendum to the fax on a drug-by-drug basis, because I'm assuming that this is not going to be the only time that you have this type of a concern or question.

Christopher Smith: That's exactly right. Thank you. Again, Christopher Smith. I think that would make it a lot easier to feel that we can ask everyone to potentially limit themselves to one agent knowing that it's easy for people to clarify the medication history.

Donna Sullivan: Correct.

Chuck Agte: This is Chuck Agte again, sorry. What I can tell you is, on the form, the form itself contains a link to the formulary listing. So, although the current design, for example, is not specific to this class of drugs. It does allow, if you're filling out the form you can click on the link and see what the formulary alternatives are that we're basically saying what we would require someone to have and then the question is worded in such a way as to, you know, basically detail for us the formulary alternatives. So, the form does contain a link to be able to identify what it is we're asking for feedback on.

Christopher Smith: Again, Christopher Smith. I don't want to belabor this, but as a very stressed clinician, I've completed these forms many times, and there is not an opportunity to go to formulary links. That just doesn't happen. It's an impossibility. We have overworked staff who also can't often figure it out on their own. So, if it's not really simple, I don't see any reason why we, as a committee, can't ask that this request be extremely simple, since we're really just looking for one question to be answered. We should just ask that question directly.

Donna Sullivan: And I think that to respond to that, Chuck and I can have a conversation, maybe offline outside of this situation or this meeting, and then we can come back to you with an alternative or potential solution, just so we don't take up this amount of time on to me what is

more of an administrative process than the actual selection of the formulary decision making. So, I think that would be… your point is well taken, and I'm assuming that we're going to have to have a process maybe not just for this particular drug class, so I'd like to maybe go back and maybe think about making it more applicable to potentially other drug classes that you might review in the future.

Barak Gaster: Alright, this is Barak Gaster. I am going to refocus us on our formulary decision on the prostaglandins for ophthalmologic use, and I would just remind the committee that this is a situation in which there have been three equally expensive, equally effective brand names available, and we now have a newly generic, much, much cheaper option, for which I can easily imagine that it is really just a matter of inertia that many patients are continuing on the more expensive brand name and that given that the overall harm to the patient would be extremely minimal and not clinically significant for them to try the generic and not respond or have an adverse effect, that my view remains that it would be better for us to not do grandfathering for this drug class and ask that physicians try switching patients to the much cheaper and equally effective generic, unless they easily respond to us that they have already done that and the patient has failed. I guess I would also say that given that this is a relatively newly generic medicine, my guess is that most of the patients who are on the more expensive brands still are not on them because they have tried and failed the cheaper generic, but because that's just what they were started on at the time when the only options in this class were three equally expensive, equally effective drugs. Other comments, thoughts?

Deborah Wiser: This is Deb Wiser, and in the big scheme of things, I would tend to agree. I think this is how we've handled other drug classes. We don't have any absolute evidence that there's less efficacy.

Barak Gaster: Anyone else want to comment?

Deborah Wiser: Deb Wiser, and I would add that given the majority of Medicaid clients that are on managed care are already in this setting, it is actually consistent with what most of Medicaid clients are already getting.

Barak Gaster: This is Barak Gaster, and anybody who is on any kind of a prescription plan formulary in the commercial world is also going to be asked to try the generic, as well.

Christine Klingel: This is Christine Klingel. If we're ready, I can take a stab at the motion. Okay. After reviewing the clinical information for the drugs within the ophthalmic prostaglandins class indicated for the treatment of the medically-accepted condition, glaucoma, I move that no single brand or generic drug product in this class has a significant clinically meaningful therapeutic advantage in terms of safety, efficacy, or clinical outcome for the treatment of glaucoma for any subpopulation. The brand of products within the class do not have a significant, meaningful clinical advantage over their generic equivalents and are excluded from the formulary in light of their clinical equivalence and after review of the average cost and drug utilization data of the medications in this class, all drugs, except latanoprost, shall be removed from the formulary in favor of less costly alternatives.

Michael Johnson: This is Michael Johnson, and I second the motion.

Barak Gaster: All in favor, say "aye."

Group: Aye.

Barak Gaster: All opposed, same sign. So, that motion passes.

Deborah Wiser: This is Deb Wiser. I just wanted to echo was Christopher Smith was commenting on regarding the amount of red tape that a physician needs to go through and when you have to do it in bulk, as the ophthalmologists will have to do in this situation, we need to do whatever we can to make this less painful. We get our requests on paper and then we hand it to our MAs, and then they fax it in, and we don't have any links, despite our electronic health records. These come in on paper.

Barak Gaster: This is Barak Gaster, and I just want to sort of point out that we're talking about 400 clients statewide that will be impacted by this decision. So, my guess is that the number of clients per physician will be relatively small and hopefully that the whole process will not be terribly painful for them.

Christopher Smith: Just again, Christopher Smith, anytime that we can update and reform the process to make it kinder and gentler, I think it will dramatically improve the view of Medicaid prescribers. People will feel like they're working with an enlightened entity that understands them and we have the same goal in mind, which is to get the right patients… the right medications in the hands of our patients and not put up unnecessary obstacles.

Barak Gaster: This is Barak Gaster. I agree completely. Any other questions, comments, thoughts? Great. So, at this point we are going to stop for lunch, and we will reconvene at 1:00 to take up the growth hormone drug class.

Duane Thurman: This is Duane Thurman. Just to be clear, I'd like to leave the committee to eat in peace and remind the committee that we should not conduct any P&T related or DUR related business during lunch. Thank you.

Barak Gaster: Alright, if everybody could take their seats, we will reconvene. So, this is Barak Gaster. We are now going to reconvene the afternoon session for the Drug Utilization Board, and the class of medications that we're going to review next is the growth hormones, and we have a speaker on the line who is going to lead us through a presentation on growth hormones. Is it Vafa Mahboubi?

Vafa Mahboubi: Yeah, thank you. Yeah, this is Vafa Mahboubi. Can you hear me okay?

Barak Gaster: Yes, take it away. Thank you, very much.

Vafa Mahboubi: Alright, thank you, and yes, we'll be focusing on growth hormone and just for the sake of completeness, there is one slide that summarizes mecasermin, as well, which ties in. Next slide, please.

So, here on slide 2, we're really looking at, in this review, and really focusing on the fact that there are multiple FDA-approved growth hormone products, and we really want to answer the question, are they identical, and can one be used to treat all approved indications, and are there any specific characteristics of one branded product over another

that we should really be preferencing over the other products that are available in this class? Next slide, please.

Slide number 3 goes over some of the background of growth hormone therapy that is appropriate when you're looking at the class as a whole. Prior to 1985, growth hormone was obtained from cadaver pituitaries actually, and it was available in limited quantities. So, really it was only used in a few indications, primarily growth hormone deficiency, obviously. Now, in 1985, there were two events that occurred, one was that there were three deaths… there were deaths in three young men that was likely to be caused by growth hormone therapy from cadaver pituitaries, and this was found to be due to prions, or the presence of prions, leading to Creutzfeldt-Jakob disease.

Since 1985, prions, or Creutzfeldt-Jakob disease was likely the cause of death in more than 50 patients who were on growth hormone therapy due to cadaver pituitaries. Obviously, it's very difficult to confirm, but this is what the data is telling us. Another event in 1985 actually coincidentally was the availability of biosynthetic recombinant human growth hormone, and this is known as somatropin. One thing to point out is that this is the exact amino acid sequence that is identical to growth hormone of pituitary origin, as seen on the right here. So, with the availability of recombinant human growth hormone, obviously it made growth hormone available in an unlimited supply compared to prior to 1985. So, from 1985 to the present what has happened is that you have multiple manufacturers, you have multiple delivery devices, there are multiple indications that it has been studied in, since its availability is not an issue anymore, but unfortunately, this has come at a high cost to consumers and payers, and this is really seen as a specialty agent with the pricing that goes along with it. Next slide, please.

So, this is slide number 4. There are multiple benefits and physiological effects of growth hormone therapy. Obviously, it stimulates hepatic production of IGF-1 or insulin-like growth factor 1, and this leads to linear growth. There are anabolic and lipolytic effects, primarily lipolysis, which leads to an improved cardiovascular health, and it alters lipid metabolism. This can lead to a decrease in LDL and triglycerides, an increase in HDL, and it has actually been shown to lower C-reactive protein, as well. It's obviously involved in

protein synthesis leading to increased lean body mass and a loss of visceral adipose tissue.

They found that growth hormone actually improves cardiac function leading to increased left ventricular mass, an increase in left ventricular end diastolic volume and stroke volume, as well. It's been linked to bone turnover, so this can cause increased bone density and ultimately leading to less of a fracture risk or osteopenia or osteoporosis. It does antagonize insulin. That is one negative effect, but alternatively patients that are growth hormone deficient, they actually have been shown to have hyperinsulinemia and insulin resistance, as well.

Studies in growth hormone treated adults, especially the elderly, has shown that it can improve mood, motivation, and quality of life and also enhance exercise capacity and it's really seen as one of those drugs that can be used off-label or abused, because it can be used for aging purposes, or anti-aging purposes, and it's also a drug of abuse in professional sports, as well. Next slide, please.

So, this is slide 5. As you can see on the left here, all of the different branded agents available, this is not all of them. These are just all of the brands. Some of them have some sub-brands underneath them, as well, but you can see that there are multiple indications now that are FDA approved for the use of growth hormone.

Most of these agents actually are indicated in growth hormone deficiency in adults and in children, and that's where you see most of the utilization when it comes to growth hormone use. One thing to point out, if you look down towards the bottom, there is a product called serostim. This has a unique indication in that it's only approved in HIV wasting, and that's in adults and pediatric patients, and then also the bottom agent, Zorbtive, this is approved for short bowel syndrome in adults only and one thing that's unique about these agents, obviously, is their indications, but also that they're used in much higher doses than the alternative agents for the other indications, as well. So, this comes into play when you're thinking about formulary placement, preferring agents, and what agents to have on a preferred drug list. Next slide please.

Slide number 6. Looking at clinical guidelines in children. In 2003, there was a publication from the American Association of Clinical Endocrinologists and also Lawson Wilkins Society in 2003, as well, and it really summarizes appropriate use of growth hormone in children. Obviously, there needs to be a diagnosis based on height and height velocity, bone age, growth hormone levels, and these are stimulated growth hormone levels. You'd like to get an IgF-1 level and also binding protein levels. Also, genetic testing to see if there's any sort of genetic disease behind the growth hormone deficiency or the patient's physical characteristics, if there are any intracranial lesions, obviously, and if there's multiple pituitary hormone deficiencies, as well.

They recommend that these agents should only be used for FDA-approved indications, obviously, and the dosing should be milligram per kilogram. The contraindications are in malignancy or in diabetic retinopathy and monitoring should be height velocity, linear growth, A1c, IgF-1, and also thyroid hormone levels, since growth hormone can suppress thyroid hormone levels. Discontinuation should be at the completion of growth, defined as epiphyseal closure or if you don't really see an effect after one year. Next slide, please.

This is slide number 7. More recently, there have been clinical guidelines going over the use of growth hormone in adults. In 2009, there was the American Association of Clinical Endocrinologists review and more recently the Endocrine Society put a review in 2011, and diagnosis really should be based on two growth hormone stimulation tests and IgF-1 levels, and a lot of these patients will be continuing therapy from childhood into adulthood and really even though they're continuing therapy, you really want to confirm the diagnosis that they're still growth hormone deficient, as adults. Also, for patients that do become growth hormone deficient as adults, you want to look to see if there's any hypothalamic or pituitary structural lesions, if there's any panhypopituitarism. Obviously, if you have any intracranial trauma or traumatic brain injury associated with any other hypothalamic pituitary deficiencies, then you want to look into growth hormone deficiency, as well.

One thing they do emphasize is that is should only be used in FDA approved indications only, and there's no evidence to suggest

treatment. Primarily, they really emphasize treatment of aging or sports enhancement. Dosing should be done in milligram per day, not per weight. Contraindications are similar. Monitoring is similar. Obviously, you want to look at thyroid levels. You want to look at if there's any adrenal suppression, estrogen levels, as well, in the sense that estrogen therapy, if you do have… estrogen levels can effect growth hormone, as well, in the sense that if you do have someone on estrogen therapy, it's been seen that sometimes you have to double the dose of the growth hormone given to the patient to see an effect. So, it is actually recommended that patients who are on estrogen therapy actually use a transdermal formulation, so it has something to do with going through the hepatic system and stimulating, probably, IgF-1 levels or something when it comes to the effect of the growth hormone.

For discontinuation, there really is no established length of therapy. These patients are growth hormone deficient and it could be indefinite, but you do want to discontinue therapy if there really is no beneficial effect after two years. Next slide, please.

This is slide number 8. Growth hormone is contraindicated, as mentioned before, in active malignancy or in diabetic retinopathy. There are metabolic complications. There can be hyperglycemia or hypothyroidism, and actually when looking at some studies or meta analyses, there has been found that there is an increased incidence of type 2 diabetes in growth hormone treated adults and children. Then, there is obviously, as listed below, multiple other adverse effects associated with therapy, as well. Next slide.

This is slide number 9. As far as looking at the pipeline for growth hormone, there are multiple manufacturers that are looking at longacting sustained formulations. This is once-weekly dosing. Novo Nordisk actually has a product in clinical trials and from what I have found in doing some research in pipeline for growth hormone is that there are multiple manufacturers actually out there looking at other longacting sustained release formulations, as well.

And just for the sake of completeness, there is one product on the market, it is a recombinant human insulin micro factor 1. Obviously, it has similar effects to growth hormone, it's just more downstream. It

is indicated for severe primary insulin-like growth factor deficiency and also patients who do develop neutralizing antibodies to growth hormone therapy, as well.

The side effects, obviously, you can have hypoglycemia, which goes along with the effects of IgF-1. It has similar contraindications to growth hormone, and it should only be used in adult patients, as well. And that's really all we have in addition to the monograph that you received.

Barak Gaster: Great. Thank you, very much.

Vafa Mahboubi: Yeah, just one thing to emphasize, going back to the adults, in the clinical guideline review for adults, especially the Endocrine Society and the AACE, is that they do emphasize that there really is no difference between these agents and that they are completely interchangeable, and obviously they are all the same recombinant product, so there is no distinction made when using one product over the other.

Barak Gaster: Great. Thank you, very much. So, I think we are also sort of very fortunate to have join us today Dr. Patricia Fechner.

Patricia Fechner: Yes.

Barak Gaster: And Dr. Fechner, why don't you sort of say a word about what your practice and background is.

Patricia Fechner: Okay. I'm a pediatric endocrinologist at Seattle Children's Hospital. I've been there for six years. I trained at John Hopkins for my fellowship and pediatric endocrinology. I have worked there and at Stanford and now Seattle Children's. I take care of children who have endocrine disorders, including short stature, and for disclosure, I have done some studies with growth hormone companies. The FDA required us to have a data registry for children who were on growth hormone when it was approved in 1986, so some of those data registries are still continuing. I have been entering our children who are in those specific growth hormones into the data registry. I have also participated in studies looking at growth hormone and trying out

different pen devices, as well as one longterm study looking at growth hormone in girls with Turner Syndrome.

Barak Gaster: Great. Do you have anything to add to the presentation that we just saw?

Patricia Fechner: I think the only thing that I might add is that there is one growth hormone that we tend to use in neonates, because it doesn't have the benzyl alcohol preservative, but other than that, we consider all the growth hormones to be equal.

Barak Gaster: Excellent. Thank you. Does anybody on the committee, at this point, have a question for Vafa or for Dr. Fechner?

Christopher Smith: This is Christopher Smith. So, all agents are felt to be clinically equivalent. Do you find, nonetheless, that there are some preferences among prescribers or patients? They say, oh this batch is better or this one stings more and I don't want to use that drug again, or are they truly indistinguishable?

Patricia Fechner: Well, biochemically, the growth hormones are the same. It's recombinant growth hormone. What's different may be the preservative that's used or the way it's administered. You can have insulin syringes we can give it, or some of the companies have pen devices. So, what we normally do is we tell the families what growth hormones are available to them on their like first tier or second tier, the most inexpensive growth hormone, and then we let the parents choose.

Deborah Wiser: This is Deb Wiser. If we were going to narrow the formulary in any way, are there certain delivery types that you would want to make sure were on there that are more or less successful than others?

Patricia Fechner: I think that a lot of families like the pen devices, because it's a little bit easier for them than having to draw it up.

Susan Rowe: This is Susan Rowe. So, I would ask sort of the same question, just for this class of drugs to me, safety seems like a really large issue. So, are there deliveries that are less safe than others?

Patricia Fechner: No. I think they're all the same. Parents can learn to give anything, and so really what determines which one they use is the cost.

Vafa Mahboubi: Yeah, just to add, really the cost is really a driving factor with these agents in the sense that I don't know how much detail to go into, I apologize, but when it comes down to tiering and formulary placement and copays, and, you know, if it's considered a specialty drug or not, or what's preferred, it really comes down to which one is going to be the low net cost for the patient but also from our perspective, from what we've seen, from the payer, as well. There are multiple delivery devices for all the agents. There's every manufacturer has a support program, as well, that's staffed by nurses, as well, that can answer questions. So, they all seem to be very similar.

Barak Gaster: Alright, this is Barak Gaster. I think that we do have two stakeholders who have requested to give comment, and then I think if you could stay on the line Vafa and perhaps after hearing from the two stakeholders we could continue discussion with both you and Dr. Fechner.

Vafa Mahboubi: Okay.

Barak Gaster: Great, thank you. So, the first stakeholder is Dr. Sue Heineman from Pfizer, and following Dr. Heineman will be Kaysen Bala. So, Kaysen, if you could be ready to speak immediately following Dr. Heineman, and Dr. Heineman, I just remind you that you have three minutes to speak and thank you for being with us.

Sue Heineman: Great, thank you very much. Again, I'm Sue Heineman. I am a Pharm.D. medical outcome specialist with Pfizer Medical. Some of the comments that have been made about the growth hormones, they are essentially the same compound, right? There are differences in their delivery systems, and also in utilization. Utilization data you guys have. It was posted out front, as well. There is also CMS data that is publicly available that I have access to. When you look at the utilization with Washington Medicaid, genotropin is one of two products that comprise 50% utilization. Nationwide, it's one of two that comprises 60% utilization, so it is a drug that is used quite often. The reason why I bring this up is that there was an article published in May of this year, Endocrine Practice, where they reported a survey of

pediatric endocrinologists for the Society. I'm not sure if you had a chance to see the survey or not, but they asked them, what was the impact in switching branded agents, or between the brands of growth hormones, and what were the results of this, and again, it's survey data. It's of the endocrinologists. Not everyone responded, but not everyone in the society actually prescribes growth hormones, and there were issues with time, cost and an average extra four hours for each practice to manage the switching. Patients, there was anxiety, there was confusion with the devices. It took a lot of almost hand holding with each of the practices to reassure the patients that, yes, it was okay to change the agent. So, there are some unintended consequences with that. There are also dosing errors that occurred. There are lapses—treatment lapses, because the patient doesn't understand how to use the device, etc. So, there are… I just ask you to consider that and in thinking about maybe having to switch someone.

What I would like to request is that at least those who are on genotropin stay on it so that there isn't any of that confusion. Again, it is one of two agents that is used in half the patients here in Washington. Additionally, genotropin covers 98% of the pediatric indications for growth hormone. So, it covers a lot of indications, a wide range of injection devices. We've got the pen that was mentioned, but we also have the only preservative-free, single-use disposable. It doesn't require refrigeration, very easy to dose, available in 10 different dosing strengths, so it's very easy for the patients, for the families to use.

Again, they talked about the support system. The Pfizer Bridge Program, we've got nurses who do the training. We have got the starter kit. There is tremendous support, and the endocrinologists, when they were surveyed on the program, 93% of them did refer their patients to that.

We also have the largest international database on patients who have been on growth hormones. It is a database that is still being mined for data. It's answering safety. It's answering efficacy questions. The 2009 clinical endocrinologist guidelines said we still need to monitor these agents even though we've got, with genotropin, over 20 years of experience nationally. So, again, I just request that you consider the unintended consequences of switching, that genotropin is an agent that

is being used quite a bit in Washington and nationally and just thank you for your time.

Barak Gaster: Thank you, very much. So, the next speaker will be Mr. Kaysen Bala from Novo Nordisk.

Kaysen Bala: Hello everyone. My name is Kaysen Bala. I'm a pharmacist and medical liaison with Novo Nordisk. Today, I just wanted to take this opportunity to talk about the growth hormone, our pen device, which is the NordiFlex FlexPro. Growth hormone therapy involves daily injections for many years. Therefore, I do want to request the committee to consider the difference in devices in your clinical evaluation of this therapeutic class.

I know Dr. Fechner talked about the chemical composition of the growth hormone. They're identical. So, with norditropin, chemically we talk about the preservative it has. It uses phenol instead of benzyl alcohol, which is contraindicated in infants. It also has histadine as a buffer, which studies have shown that histadine is not associated with any injection site reaction, such as stinging or burning.

So, actually with the pen device, I do have a demo pen device to show to you. This is the norditropin FlexPro and it's prefilled, premixed, multi-dosed disposable pen. So, it's quite easy for patients to learn and use. It does not involve any reconstitution, does not involve any mixing or loading of cartridges or batteries. It also has a unique feature of storage flexibility in that the 5 and the 10 mg FlexPro pens can be stored at room temperature for up to three weeks after initial use. This is convenient for patients when they have to travel or can potentially reduce waste if they forget to put the pen back in the refrigerator.

It also has small fine dosing increments. The 5 mg FlexPro can be dosed to 0.025 increments, so this allows flexibility for the physicians to optimally dose their, especially their pediatric patients, who are weight based. Therefore, also potentially reducing any wastage of product.

So, to use the product, you know, the patient will simply remove the cap, install the needle, and then dial to the appropriate dose, and if they

go too far, they can go back. You can hear the sounds, and it's actually intentional auditory signals to let the patients know that they are going forward and backward and to administer they will press on this white button, and there's also another auditory signal. It's an end-of-dose click so that the patient knows that the medication has been administered.

Finally, I do want to talk about the support services program that Novo Nordisk has for the FlexPen patients. It's called Nordicare. The NordiCare program has case managers that are fluent in English and Spanish, can provide reimbursement support, provide education materials, and coordinate with the patient's free in-home injection training.

Also, the presentation sort of talks about the FDA approved uses and also the potential off-label uses. Our support program, NordiCare also acts as a gatekeeper, so we ensure that all the patients who go through our program are FDA-approved indications. So, when they see the prescriptions come through, they assess all the labs and make sure they are FDA-approved indications. They are essentially our gatekeepers, as well. So, I do want to thank you for our time, and if you have any questions I can address them at this point.

Barak Gaster: Great, thank you very much.

Kaysen Bala: Thank you.

Barak Gaster: Alright, so this is Barak Gaster again. So, I guess one of the issues that will be the most difficult for us to tackle is to identify what we want to put in the formulary as the medically-accepted conditions that our formulary are going to apply to, and this is a class of medications in which the medications themselves are interchangeable but for which the indications for which they can be used is complicated. Before we get there, is there any more questions that people have for Vafa on the line or for Dr. Fechner who is here with us?

Eric Harvey: This is Eric Harvey. I just… it's more of a comment than a question, and it is related to the method of delivery of the dose of this medication. I think because, especially for our pediatric patients, we have the caregivers actually drawing up the dose. That creates extra

risk in this situation, and I would like the committee to consider having some device… some injectable device available for the use in those patients so that we're not obligating our families to draw doses out of a vial if there's another device available.

Barak Gaster: Excellent point. I guess a question that I have that is, that maybe Dr. Fechner knows the answer to, or maybe Donna knows the answer to, which is trying to understand the cost of these drugs and that if they are all so similar, is there patent protection or sort of… on the claim data that we have here, one of them is sort of extremely inexpensive, presumably due to a rebate. Is that a fixed sort of feature of that particular brand? Or is… how does the cost of drugs in this class work?

Donna Sullivan: This is Donna Sullivan. So, the majority of our utilization is in the pediatric population. So, with it being… then if it's a weight-based dose, it might be dependent on, it might be younger children using one product versus another product. With the Tev-Tropin, it is across the market typically priced cheaper than the other products. The Saizen Easy Click, I'd have to dig in and see why that's coming up negative. I wouldn't have expected that to be a negative number. The other Saizen I think is only being used in two clients, so I think it has to do more specific to whose using it and the dose that they're giving. Dr. Fechner, did you have anything to add?

Patricia Fechner: So, usually when I hear about the costs, I hear that the cost is how many dollars per mg, so that's probably a better comparison, because as you said, maybe different ages use different… smaller children don't need as much growth hormone as a larger child does.

Barak Gaster: Yeah. This is Barak Gaster. Are you aware that there are big cost differences per mg among the drugs in this class?

Patricia Fechner: I know that there is some variation, but a lot of it depends just on what they negotiate with what insurance company, some of it is also.

Barak Gaster: Yeah, okay.

Donna Sullivan: This is Donna Sullivan. So, the different plans would have different rebate agreements. So, these again are including our federal rebates, net of federal rebate.

Patricia Fechner: Can I interrupt one second? Not all of them are still available, so it's not an updated list.

Barak Gaster: Okay.

Vafa Mahboubi: Dr. Gaster, from the ones that are still available, there is a variation if you look at cost per mg. That can be pretty wide. So, it is one thing that you would want to do an analysis on, on top of looking at what other opportunities you have available through your industry relations.

Barak Gaster: So, this is Barak Gaster. I guess I'm struck by the fact that we're hearing that all the drugs in this class are relatively interchangeable, that there are differences in their delivery mechanism but that several different brands have acceptable delivery mechanisms, and so then it would end up coming down to cost for us to try to make some formulary decision, but we don't really have information on what the cost to state Medicaid would be per mg. That the claims data that we have here is not necessarily representative of what the cost to state Medicaid would be.

Donna Sullivan: It's representative of what it's currently costing us on a daily basis. So, these are the current costs per day based on what's being prescribed to the patients that are currently receiving it, but yes. I can't predict what it would cost in the future if the patient's mix changed, and I want to emphasize that this does exclude anybody that has been shifted to managed care. So, these are the clients that were remaining on our fee-for-service program so we don't have to worry about that particular shift of population, but it is the majority of our pediatric use, and they will be aging, as we go forward.

Barak Gaster: This is Barak Gaster again. It's a very different situation than for instance with the prostaglandins that we just finished reviewing where there was one generic, which was clearly easily tabled to be predicted to be much less expensive than the others, but that's not necessarily the case for this class.

Donna Sullivan: It's more difficult to tell based on the way that we did the cost analysis, yes. I would agree with that.

Susan Rowe: This is Susan Rowe. Can I ask a question of the other pharmacists, maybe? The pens versus the cartridge that I assume goes into an injecting device, are they both similarly easy to use?

Eric Harvey: This is Eric Harvey. Generally speaking, yes.

Christopher Smith: This is Christopher Smith. Is there a reason, and I have experience with insulin injection devices, but with these pens or just syringes and drawing up the solution, is there any reason why you'd still want to have a syringe? Maybe some adult patients would not want a click pen or some other device? Can you think of a reason why we wouldn't want to overly concentrate into one delivery system?

Patricia Fechner: Almost all of my patients prefer using the pen device. I have maybe 1 out of 50 who like it and it was only because he had certain psychological needs, and it empowered him to be able to draw it up as opposed to, but almost every other patient prefers a device where they don't necessarily see the needle or they don't have to draw it up. It's less stress for the family.

Donna Sullivan: So, this is Donna Sullivan. So, what I'm hearing, Barak, if you would like, we can go back to the drawing board and take a look at the data and calculate out the cost per mg and bring that back to you, if you would prefer to do that and revisit this in February.

Barak Gaster: This is Barak Gaster. I'm just hesitant for us to make decisions here based on cost without a good sense of sort of what the true costs are going to end up being going forward. So that would be my recommendation.

Eric Harvey: This is Eric Harvey. I had just one suggestion to consider, and that would be maybe we can nail down or at least define what the indications for use are at this meeting, since we have an expert here to help us with that, and then at the next meeting, it's really just a decision about which product.

Barak Gaster: Great.

Christopher Smith: Christopher Smith. I have one other thing we might add to today's discussion and that was the concern was brought up that in changing patients it creates a lot of confusion and anxiety, and I also heard, however, that there is tremendous support on the industry side and certainly in the clinics where this is prescribed. So, I wanted to get your input, Dr. Fechner, about the challenge to switching agents. Is that unfair to ask patients to switch?

Patricia Fechner: Well, I think it's extra work for the family. It's also extra work, as she said, on the part of the physician's office. We don't get paid for filling out authorizations, reauthorizations. We don't get paid for teaching families. So, if a family goes from one device to another device and it's significantly different and they can't figure it out on their own, they need to come in to see us or a nurse has to go out to see the family. So, it does take extra time. The devices are a little bit different, so it could cause confusion and mistakes could be made.

Christopher Smith: Christopher Smith, again. At the same time, you did refer to the fact that some patients have formulary issues that you already deal with, so you have skill and experience with patients being required to do this by other payers.

Patricia Fechner: We do. Some insurance companies change what is on their formulary based on cost, so we have to switch them. There are sometimes periods when a family may not get the growth hormone for a month while the paperwork is in process, the reauthorization is going on, and that can also be hard for a child who's used to getting a shot every day. They stop getting the shot, then having to reintroduce it. It's not always something they want, so it's sometimes difficult to restart it.

Christopher Smith: Christopher Smith. So, if we were to expect that of patients, we would certainly have to make sure there's no interruption in therapy, as we've been assured would be the process that the state would follow. That would, hopefully, remove that one element of the change.

Patricia Fechner: Right.

Barak Gaster: This is Barak Gaster. So, Eric, since you brought up the question of deciding about conditions, do you have thoughts about how we would approach that question?

Eric Harvey: Sure, I'll take a stab at it and I'm sure Dr. Fechner would be welcome to chime in where I mess up, but I would start with growth hormone deficiency, Prader-Willi Syndrome, small for gestational age with fail to catch up by two years, Turner Syndrome, idiopathic short stature.

Patricia Fechner: Okay, so SHOX deficiency is actually very similar to Turner Syndrome in the sense that the gene on the X chromosome is what's causing short stature in Turner Syndrome. So, I would say that SHOX deficiency is a gene diagnosis and should be included if you're going to include Turner Syndrome.

Eric Harvey: This is Eric Harvey. I would agree with that.

Christopher Smith: Christopher Smith. We can't leave out the adults, right? So, adult growth hormone deficiency would also be an indication.

Eric Harvey: This is Eric Harvey. Yeah, when I said growth hormone deficiency, I was just stating it globally so that it would include all patients with growth hormone deficiency. That was my intention.

Christopher Smith: So, if these products are equivalent, to what extent do we have to limit ourselves to those that have FDA approval for each indication?

Patricia Fechner: We use them interchangeably. We first, though, try to look at the formulary to see what's FDA approved, but if something's not FDA approved but it's on their formulary, we'll give them the cheaper drug—the less expensive drug, because we do feel that they are the same, but I think that the drug companies, if it's not FDA approved, may not be able to support that indication, as well.

Deborah Wiser: This is Deb Wiser. What do you mean by the drug companies can't support it?

Patricia Fechner: Well, you… we had mentioned that the drug companies have like the bridge program or whatever programs they have to support assistance or to answer questions. I don't know if they're going to be able to do

it if you're giving it for an indication that's not approved, because they can't… they'll get in trouble, perhaps, with the FDA.

Barak Gaster: This is Barak Gaster. I think that the issue about the FDA approval for the drugs that we list in our formulary is important. I mean, we… the formulary that we are charged with coming up with is different than the formulary that a commercial payer would face in that a commercial payer does not necessarily need to come up with indications for each of the drugs that they are placing on their formulary. So, I think… so, for instance, if we include the diagnosis of SHOX deficiency in our formulary, then we are then kind of required to include the one drug, which is FDA approved for that condition whereas if we leave that more restrictive diagnosis out, then anybody who has SHOX deficiency is sort of free to use any drug that's in the class, but we are less restricted in deciding what drug we actually place on our formulary based on cost.

Donna Sullivan: This is Donna Sullivan. So, the use of… when you look at somatropin in the compendia, it is supported across all of these indications in the compendia, even though it doesn't… not each product has this specific FDA indication. So, I don't… I think that since the federal statute says use FDA labeling and the compendia or supported in the compendia, I think you're okay with that.

Barak Gaster: Okay, great. So, this is Barak Gaster. So then, I would just sort of clarify for the committee that the very detailed table that we have in front of us of FDA approvals does not necessarily impact our decision making about our formulary.

Donna Sullivan: No, this was provided just for your review.

Barak Gaster: Thank you.

Deborah Wiser: This is Deb Wiser. Does that also apply to Tev-Tropin, which does not seem to have adult dosing?

Patricia Fechner: Growth hormone is growth hormone. It's the same growth hormone.

Barak Gaster: So, this is Barak Gaster. Then, I guess I'm wondering why not include all of these diagnoses in our formulary? What is the consideration one way or the other for leaving a diagnosis off or including it?

Donna Sullivan: This is Donna Sullivan. So, Dr. Fechner, can you respond to that question maybe as it relates to Increlex for the two indications with that medication? Do you consider that similar to the growth hormones, or…?

Patricia Fechner: I do, and then I just want to say I don't treat chronic renal insufficiency, so that's why… but I know that our nephrologists do, so they use growth hormone for that indication, but we as endocrinologists don't see patients with that diagnosis. So, I can't comment on it.

Barak Gaster: So, this is Barak Gaster. So, I'm just sort of throwing out the idea in this sort of tricky decision that we have of what conditions to list in our formulary motion that I'm not seeing but somebody correct me if I'm wrong, a down-side to just including all 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14 diagnoses that growth hormone has an indication for.

Susan Rowe: This is Susan Rowe. I guess I would ask, as I look at a couple of the indications, I'm wondering if growth hormone is actually the primary treatment for some of these indications. So, that I'm not sure about.

Patricia Fechner: So, for a child who is growth hormone deficient, it is. For Turner Syndrome and SHOX Syndrome, studies have shown that use of growth hormone… these children are maybe eight inches less than expected if they don't have growth hormone, and with growth hormone you can increase their height to very close to what you'd expect for mid-targeted height. There's nothing else we can give. Studies have shown it helps also in Prader-Willi and the SGA. I think idiopathic short stature is maybe a little bit more difficult. Studies have shown there that they can gain a centimeter.

Susan Rowe: This is Susan Rowe. Let me apologize. I didn't mean for the initial… I'm talking about things like HIV fat maldistribution, chronic kidney disease. Some of the other indications that we're considering including is growth hormone your treatment of choice there? HIV cachexia?

Patricia Fechner: That's outside of what I see, because I see pediatric endocrinology, and that's not really pediatric endocrinology, so I can't answer.

Donna Sullivan: This is Donna Sullivan. So, I was going to point out that the HIV fat maldistribution, it's not indicated in the compendia and that it's only recommended for some patients but not most. So, it had the weaker evidence, and I think Nicole looked it up. She might be able to speak to it better about what the information actually said, but that is one thing where it's not really indicated but it is used, and the evidence isn't necessarily very strong supporting it.

Barak Gaster: This is Barak Gaster. Again, if we leave one of these diagnoses out, it in no way precludes Medicaid fee-for-service clients getting their growth hormone paid for, right?

Donna Sullivan: I'm sorry. Say that again, please.

Barak Gaster: If we leave one of these diagnoses out, it in no way precludes a Medicaid fee-for-service client getting their growth hormone paid for, for that indication.

Donna Sullivan: I think that's right. If you leave an indication out, then that drug would be formulary for its FDA labeled indications.

Chuck Agte: Yes. This is Chuck Agte. If… just to pick one at random, if for example you did not address Noonan Syndrome in your decision in some way, then… and norditropin for example was not one of your formulary selections, then it would leave a situation where norditropin may not be on the formulary but we would have to ensure we allowed it for Noonan Syndrome.

Nicole Nguyen: This is Nicole Nguyen. I just wanted to add to that. What we see coming through Medicaid is mostly the endocrine, the main diagnosis Noonan isn't as common I don't think. I see chronic kidney disease and adult growth hormone. The HIV wasting, that is serostim, and I rarely see that and the Zorbtive for short bowel syndrome. I have maybe seen one in the last few years. So, it's mainly going to be these endocrinology type and the renal disease is another one that I see quite a few of.

Barak Gaster: So, this is Barak Gaster again. So I'm still not sure that I feel very clear on which indications we should include or which we should exclude. I think it's… anybody have a line on this?

Deborah Wiser: This is Deb Wiser. I feel like there's a question mark around the use of these agents for chronic kidney disease and whether that's for second, third, or fourth line, and I feel like we need more information on that.

Donna Sullivan: This is Donna Sullivan. So, I just want to mention that we do have a nephrologist coming in to talk about the ESAs at 2:30. So, we might be able to use a little bit of his time to talk about that, as well. I didn't realize that chronic kidney failure, when I was looking at it, was an indication for the growth hormones. Otherwise, I would have brought him in sooner. That's not the nephrologist that we're bringing in.

Barak Gaster: So, let… I think… this is Barak Gaster. We have decided already to put on hold the question of which drugs pending better cost information. We've made an attempt to think about which indications, but I think… and we have an idea that it will probably be most of the indications that we have listed here will be included in our formulary motion, and we will return to this drug class in February.

Christopher Smith: This is Christopher Smith. We do need to define some medications though, don't we? We don't want people using it in a situation where it wouldn't be indicated ordinarily, for instance, for weight control or for bodybuilding.

Chuck Agte: This is Chuck Agte. Depending on how you word your decision, you could get around that, but Medicaid is already barred by other rules from paying for anything that is not either FDA labeled or supported in the compendia. So, you don't… those are… the type of use you're talking about, regardless of your formulary decision, we're not allowed to pay for anyway.

Barak Gaster: Alright. So, I think especially at this point, we can let Vafa go. Thank you very much for joining us.

Donna Sullivan: I think he's already gone.

Barak Gaster: Great, and once again, thank you so much, Dr. Fechner, for being here and for your input. So, that will close our discussion for now on the growth hormone class. Donna, tell us what happens next.

Donna Sullivan: We need to take a short break and discuss the agenda.

Barak Gaster: Great. In terms of when to reconvene, though, should we say…

Donna Sullivan: We can do 10 minutes, 15 minutes.

Barak Gaster: Great. So, let's reconvene at 2:05 p.m., in 10 minutes, and thank you all very much.

Alright, so now we are reconvening. This is Barak Gaster. We are reconvening the Drug Utilization Review Board and we're going to talk about erythropoiesis-stimulating agents, and I believe we're going to start first with some information about Omontys.

Chuck Agte: This is Chuck Agte, and currently outside of the formulary considerations, because at this point it's not part of the formulary yet until you guys make a decision in regard to ESAs, Omontys is the… let me pull up my criteria here. Currently, for the erythropoiesis-stimulating agents, we do not have authorization criteria on three of the drugs in the class, but we do have authorization criteria on Omontys, and Omontys is the newest entry into the class, and the majority of our criteria is around, is it being used for its FDA indicated indication? The additional part of our criteria is that our clinical staff at the time that it was originally reviewed made a determination that other ESAs needed to be tried prior to Omontys, and I'm going to let Nicole speak to some of the specifics of that, but we are looking at whether or not that is appropriate criteria for Omontys or not. I believe we may have stakeholder input regarding that, as well, and I'd like to go ahead and turn it over for the moment to Nicole, because she was part of the review team that came up with the criteria originally.

Nicole Nguyen: Okay. This is Nicole Nguyen. I think we reviewed Omontys in the spring, I think in April, and when it was reviewed, it was around April that we reviewed it. It was decided to keep it on PA and part of the criteria was to try and fail the other drugs in the class, and it's mostly a

safety… it was more of a safety concern with the new drug versus a cost. It's kind of hard… we had a hard time reviewing costs because different patients will be using different amounts. So, when you look at the ranges that someone could possibly be on, it was hard to tell. It might be a little more… we thought it might look like… I mean lower doses might be a little more expensive but less expensive higher doses. So, it's kind of hard to tell. I don't know. I haven't looked at what we've come up with costs for this review. A concern was that it had narrower indications where the other products have indications for patients on myelosuppressive cancer chemotherapy. They have for kidney disease in patients that are not on dialysis, and a couple of other indications, too. This one is only four patients who are on dialysis, and it's not recommended if they're not on dialysis because of safety concerns. There is a study comparing to an active control where with this drug there was higher cardiovascular risk with it. So with that, with it being a brand new drug, and it's just coming out from clinical study into our general population, we were kind of conservative. We decided that the other ones have had safety concerns. FDA has put alerts at using lower doses over the years and limit in the cancer utilization and risk communication, and so due to that, the safety concern of it is it has a narrow indication, and there's the concern there was some risk in the non-dialysis population. What if it goes out in the general population? Some more risk comes after market. It's been on the market now for awhile, and I know that there's people here to talk more about it. So, it's something that we would be coming up to review soon, so I would like your guys' help and input back on if… how we need to treat all of these and if there are any of them that need to be treated differently or not, and if we need to change our criteria on it. I know in the past, I think it was in 2008 I think was when they first came out the FDA looking at ESAs, and I think we might have brought it to the DUR board then, and what we did with the products that were available then we sent out provider notice just telling them that this is what is being recommended. You only use it when the hemoglobin gets to this level and just kind of a provider notice, and from our utilization of the products, it looks… I haven't looked in depth. I know recently when I was looking for rebates, this last year they put out… the FDA put out further recommendations on dosing, using lower doses. I was sent rebates because they were seeing a difference in utilization. So, I did see that it looked like… their concern was that they thought there was being used more or less, but when I looked at

it… when I looked at the data, it looked like they were moving from using the higher vials to the lower dose vials. So, to me, I thought well, it made sense that our providers were listening to the FDA and were trying to use lower doses, and that was encouraging. Anybody have any further questions?

Chuck Agte: So, this is Chuck Agte again. In regard to some of the concerns that we originally had, we have received information, and I'm sure someone with Omontys could probably comment on this better than I can, but some of the concerns originally about whether or not it might be used in a nondialysis population, I believe that the manufacturer has significant controls around when Omontys goes out to begin with. I think they have their own programs that ensure that its use is restricted to clients on dialysis and in regard to cost, we don't have cost on this drug calculated at this point, because we haven't seen any utilization at this point. One of the complaints we're receiving is that based on our criteria, there will never be utilization. So, we have had the biggest… the point of contention in regard to our criteria is whether or not it is reasonable to require the use of a different ESA and then allow them to change to Omontys. Some of the feedback we have received is essentially that the ESAs work more or less. There is generally very little situation where someone would start on one and not continue to use that same drug anyway. So, that is part of the challenge in regard to our current criteria, because again, that criteria is based predominantly around is it being used appropriately by FDA indications and then the requirement of whether or not they've tried another ESA. So, that would be the part that we're looking for additional guidance from the board is, and you may need to wait until you have the additional consultant to refer to as well, but we're requesting your feedback specifically in regard to whether or not there should be a condition for the trial of a different ESA before moving onto Omontys.

Donna Sullivan: This is Donna Sullivan. So, just to let you know that if you want a little bit more information about the safety concerns with Omontys in the nondialysis patients, it's summarized starting at the bottom of page 12 in the monographs where in the Pearl Study that the treatment with Omontys was associated with an increased risk and composite safety endpoint of death from any cause or cardiovascular event consisting of myocardial infarction, stroke, or serious adverse event of congestive

heart failure, unstable angina, or arrhythmia, and then it goes on to discuss some of the other safety issues that were found in that particular study. So, that was really the reason why, or the founding factor of us putting it on prior authorization and making them try one of the other ESAs prior to Omontys.

Barak Gaster: Okay. Thank you very much. Why don't we, at this point, hear from two stakeholders. The first will be Dr. Krishna Polu from Affymax and following that, please be ready to speak, Dr. Vinson Lee from Amgen. So, let's begin with Dr. Polu. I'll just remind you that you have three minutes.

Krishna Polu: Okay. Thank you. I appreciate the opportunity to address the Drug Utilization Board for Washington Medicaid. My name is Krishna Polu, and I'm a nephrologist and the vice president of clinical development at Affymax Incorporated. As you are aware, ESAs have been on the market for over 20 years for the treatment of anemia. The FDA approval of Omontys represents the first time in that 20-year period that a new ESA has been widely available to treat anemia in the dialysis setting. I am here today to address the restrictive coverage decision by Washington Medicaid made by Washington Medicaid denying patient access to Omontys for the use of patients in adult patients with CKD on dialysis.

This restriction was made by the pharmacy department leaving the state to place a clinical edit on Omontys requiring the failure of Epogen and Aranesp prior to the usage of Omontys based on their perception of increased cardiovascular risks.

As background, I was directly responsible for the completion of the phase 3 clinical trial program evaluating the safety and efficacy of Omontys in dialysis and nondialysis patients with anemia due to chronic kidney disease. I was also involved in the filing of the new drug application to the FDA and participated in the discussions with the FDA regarding the safety, efficacy, and risk-benefit assessment of Omontys for the treatment of anemia in patients on dialysis. On December 7, 2012, I also presented the risk-benefit assessment to the FDA Oncology Drug Advisory Committee, or ODAC, made of up an independent group of experts, including oncologists, hematologists, nephrologists, and cardiologists. This committee voted 15 to 1 with 1

abstention in favor of a positive benefit-risk assessment for Omontys in dialysis patients supporting the ultimate approval of the drug by the FDA on March 27, 2012.

We believe that your decision to restrict Omontys coverage due to cardiovascular safety concerns is unwarranted and in direct conflict with the FDA approval of Omontys and a broader assessment by clinical experts in the field. It is important to note that Washington Medicaid is the only payer of any type in the country to restrict Omontys for this reason. During the NDA review period, Affymax addressed similar cardiovascular concerns regarding the safety of Omontys, the benefit-risk ratio in dialysis, the implications of the nondialysis safety results, which you've discussed today, and the evaluation of long-term safety. The data in the Omontys Development Program was the most extensive clinical program in assessing safety, particularly preclinical toxicology and clinical cardiovascular safety of any ESA ever filed in this country. Thus, our ability, as well as the FDA and ODAC, to critically evaluate the safety of Omontys in dialysis patients relative to other ESAs, including the implications of the nondialysis results, was strengthened by the availability of a robust data set from the largest active controlled clinical trial experience of an ESA. In this assessment, it was found that none of the adverse cardiovascular safety findings in nondialysis patients receiving Omontys relative to the ESA comparator were duplicated in the dialysis patient population who, in general, are sicker and a higher-risk population for cardiovascular events. The dialysis trials were also large in size, larger in size, than the nondialysis trials, further giving Affymax the confidence that the data supports a safe and effective use of Omontys to treat anemia in patients on dialysis.

In conclusion, our assessment, as well as that by the FDA and the ODAC support the safety and efficacy of Omontys for the treatment of anemia in adult dialysis patients. To support dialysis provider requests and to help remove reimbursement barriers often associated with a new drug, CMS issued a product-specific q-code upon the FDA approval of Omontys. Affymax and [inaudible] have been working with the various departments of Washington Medicaid since the FDA approval of Omontys on March 27th of this year with no avail. It has been almost nine months since approval, and we have respectfully followed the process in place, and dialysis providers have asked for

access and Omontys and coverage continues to be restricted. In addition, ODS and…

Barak Gaster: I'm going to ask you to complete your remarks, please.

Krishna Polu: Okay. ODS and MedImpact conducted an independent, unbiased review of the ESA class, Omontys in particular, was presented at the October 17th meeting here, and it's concluded in this review that Omontys was as safe and efficacious as other ESAs on the market.

I am respectfully asking Washington Medicaid to remove the barrier immediately, as it is unwarranted and does not reflect the opinion of the FDA or ODAC. At this time, I am open for questions.

Barak Gaster: Thank you, very much. Next, we will be hearing from Dr. Vinson Lee at Amgen.

Vinson Lee: Good afternoon. Thank you for the opportunity to speak today. My name is Vinson Lee, and I'm a pharmacist and health outcomes regional medical liaison with Amgen. I understand there's a three-minute time limit, but due to the fact that we – Amgen – represents two products, I know that we've respectfully asked for some additional time to discuss both products, since both of them are under review today.

Amgen has already provided you with key clinical information prior to this meeting. You should have it that already in your packet. I want to take just a few minutes to highlight some of the information for each of the ESAs individually starting with darbepoetin alfa, brand name Aranesp.

In the nephrology setting Aranesp has an FDA approval for the treatment of anemia associated with CKD, including patients on dialysis and not on dialysis. Aranesp has a serum half-life that is approximately three times longer than epoetin alfa, and in patients with CKD on dialysis, Aranesp is dosed once weekly or once every two weeks, and in CKD patients not on dialysis, Aranesp is administered every four weeks reducing the number of injections and potentially overall cost of care. Aranesp is also available in single-dose vials to be administered IV and single dose prefilled syringes to

be administered subcutaneously. Aranesp is also approved for the treatment of anemia due to the effects of concomitant myelosuppressive chemotherapy and upon initiation there is a minimum of two additional months of planned chemotherapy. In this setting, Aranesp is dosed once weekly or once every three weeks, which allows Aranesp to be synchronized with common chemotherapy regimens that are dosed every three weeks reducing the number of injections and potentially the overall cost of care.

In the chemotherapy-induced anemia setting, clinical trials by Glasby et al for Procrit and Canon et al for Aranesp that demonstrate similar efficacy. Comparative cost analyses based on these clinical trials have reported a comparative advantage for Aranesp over Procrit in the overall cost of care.

In 2011, in collaboration with the FDA, Amgen modified the label for Aranesp to communicate the revised benefit-risk profile of the ESA class. This information is applicable to the entire class of ESAs, and the modified PI language includes changes to the box warning and informs the safety risks that have been identified in clinical trials. The label no longer recommends a specific target hemoglobin range but rather individualized dosing and provides recommendations for the initiation of therapy and guidance for dose adjustments.

In summary, for Aranesp, it has been used extensively for the management of anemia having more than 10 years of clinical experience. This longterm experience is important in a class of products where dosing is recommended and individualized to the lowest dose sufficient to reduce the need for red blood cell transfusions.

I thank you for the opportunity to provide information in support of the implementation of a policy aligned with the current Aranesp prescribing information, and I respectfully ask the committee to maintain Aranesp on the formulary, as it has been, to continue to allow patient access to Aranesp.

I would now like to switch gears a little bit and take a few minutes to highlight information for the ESA, epoetin alfa, brand name Epogen.

Epogen has multiple indications across the board, including treatment of anemia due to CKD in patients on dialysis and not on dialysis, zidovudine in HIV-infected patients, and the effects of concomitant myelosuppressive chemotherapy.

Epogen is marketed by Amgen for the treatment of anemia associated with CKD in patients on dialysis. It provides a three times per week dosing that can be aligned with a three times per week hemodialysis treatment schedule used by the majority of chronic dialysis patients. This dosing schedule of Epogen provides frequent opportunities to respond to hemoglobin changes due to the wide range of clinical complexities in patients on dialysis including patient factors and comorbidities, intercurrent events, and practice patterns.

Again, in 2011, to reiterate our safety issues, in collaboration with the FDA, the label was also modified for Epogen to communicate the revised benefit-risk profile of the ESA class. Again, this modified PI includes changes to the box warning and informs of safety risks that have been identified in the clinical trials. We reiterate the fact that the label no longer recommends a specific target hemoglobin rate but rather individualized dosing and provides recommendations for the initiation of therapy and guidance for dose adjustments. Given these recent changes to the label, historical claims data may not reflect current or future practice patterns, which should also influence previous claims cost analyses.

In summary, Epogen and Aranesp have both been used extensively for the management of anemia, having more than 20 years of clinical experience for Epogen. Again, this longterm experience is important in this class where dosing is recommended to be individualized. I thank you, again, for the opportunity to provide information in support of a policy aligned with the current Epogen prescribing information, and I also respectfully ask the committee to maintain Epogen on the formulary, as it has been, to continue to allow patients access to Epogen.

Barak Gaster: Great, thanks very much. Alright, this is Barak Gaster, and at this point, we are almost ready to have on the line a nephrologist expert who has been arranged to speak with us, Dr. Clayton Smiley who is scheduled to join us at 2:30. Is that right?

Donna Sullivan: This is correct?

Barak Gaster: Great. Do you know, Donna, did he have a presentation prepared for us or was he just going to be available for questions?

Donna Sullivan: I think he was just going to be available for questions. He was provided with the monograph and the slides that were presented at the last meeting and would be able to address any questions that you had for him.

Barak Gaster: Okay. This is Barak Gaster still, I guess this is likely going to end up being a somewhat analogous situation to the growth hormone class, in that the medications in the class are all pretty similar in their efficacy, they differ in their delivery in terms of how frequently they must be dosed and so it will end up coming down a lot to what the relative costs will be to Washington State Medicaid fee-for-service program. So, while we're waiting for Clayton Smiley we can look at the product utilization data that we have before us, which as Chuck mentioned, does not include any information on Omontys, as Omontys has not had any utilization. But then even trying to compare the drugs that we do have data on here, I guess one of the things that strikes me is that this is a very tiny number of patients, less than 100, something like 100 clients statewide, which is clearly a pretty tiny fraction of the people in the state who are getting any of these drugs.

Clayton Smiley: Hello, this is Dr. Smiley.

Barak Gaster: Good afternoon, Dr. Smiley. My name is Barak Gaster. I'm the chair of the Washington State Drug Utilization Review Committee, and we are gathered here today to review the class of erythropoietin-stimulating agents, and we are very grateful to you for joining us.

Clayton Smiley: Happy to help.

Barak Gaster: Why don't you begin giving us a little bit of background about your background and then we'll continue our discussion.

Clayton Smiley: Okay. I am a nephrologist. I went to medical school at the University of Chicago. I did my residency training at the Naval Medical Center

in San Diego, and I was the chief of residents for a year there at that hospital, and then I did my fellowship training at UCSD for two years, and then the navy sent me to the Naval Medical Center in Portsmouth, Virginia for an additional three years, and I have been in Portland, since July of 2007. I'm the medical director of the Gresham Innovative Dialysis Services unit and the St. Helens Dialysis Unit for Fresenius Medical Care, and I am also in charge of our research for our group with the NW Renal Clinical. We're the biggest nephrology group in Oregon.

Barak Gaster: Excellent. Thank you so much. Can you give us a little bit of info about any connections you have to the pharmaceutical industry?

Clayton Smiley: None.

Barak Gaster: Thank you.

Clayton Smiley: I don't receive… I have friends that are in the industry, but I receive no monetary compensation from anybody.

Barak Gaster: Great. Alright. Thank you. So, let me sort of complete the thought that I had going there just before you came on the line, which was that we were just reviewing the utilization data that we have for Washington State fee-for-service Medicaid on the number of claims for the ESAs, and it looks like the total number of claims and total number of clients that would fall under our formulary decision is a very small group. Is that right, Donna? Am I missing something?

Donna Sullivan: Yes. We have approximately 100 patients that are on the ESA products, and the majority of those are using it for chronic kidney disease.

Clayton Smiley: Okay.

Barak Gaster: Then also noticing that it's a little bit tricky to really tell from such a small number whether there is really a… and from the way that the data is presented here, it's difficult to really get a sense of what the cost differential is, because of the potential differences that there are in the way that the different drugs are being dosed. Is that also right, Donna?

Donna Sullivan: It is. I want to point out that the numbers that are… the number that to me sticks out as being kind of a little questionable is the Procrit. There were only three clients that had Procrit for a total of seven claims, and it comes out to be $98.68. So, that is an anomaly with that particular utilization. I would expect it to be up closer to the $400 or $700 per dose, or per claim. So, again, based on the types of data or the claims that were there, I don't know if this was a small child that it was used in that would have gotten a much smaller amount than an adult patient. So, it is a little bit different. We're struggling with this particular class on the cost. So, we looked at it by claim. I don't have, at this point in time, like the frequency of are these being given weekly versus monthly between the different drugs, as well, as far as our claims data. We didn't get down to that level.

Barak Gaster: Okay. This is Barak Gaster. So, once again, we're left with a class of medications in which the agents are likely of similar efficacy, so then it really, any formulary decision would ideally really come down to cost, but it's really hard for us to make a cost-based decision given the data that we have.

Donna Sullivan: This is Donna Sullivan. I just want to say that I'm pretty confident of the price difference between the Epogen and the Procrit for treatment of chronic renal disease within dialysis. That is where they are a very similar medication and they're getting it three times a week when they go in for their dialysis sessions. So, I can say that is, I think, a very valid comparing of those particular products. The difference would be more when they're using it with anemia due to chemotherapy and how often they're actually dosing that particular product.

Barak Gaster: Thank you. So, this is Barak Gaster. So then if we are to drill down on that specific indication of renal failure with dialysis for Epogen versus renal failure with dialysis for Procrit, the cost per claim is $662 versus $492.

Clayton Smiley: For which? Which is which?

Barak Gaster: So, the Epogen ends up being $662 per claim, but that's for five claims, and Procrit is $492 per claim, and that's for 40 claims.

Clayton Smiley: Is the claim based on the amount of drug given, because typically that's how, at least in our group, we use Procrit in our group and when we send the bill to whoever it is we send it to, it's based upon the dose given, not necessarily the encounter.

Donna Sullivan: Yes, Dr. Smiley, this is Donna Sullivan. That's exactly what we did. We took the medications. We looked at the amount of drug that was… the amount that we actually paid for that particular product in that claim. So, this is the cost of the product itself, net of its rebate, and not the cost of the actual visit.

Clayton Smiley: Okay.

Donna Sullivan: And I do want to say that the Aranesp data, I'm confident that that is how much it is per claim, but then we just don't know if it's being given twice a week versus monthly.

Clayton Smiley: Right.

Barak Gaster: This is Barak Gaster. So, Dr. Smiley, can you… so I guess our questions to you really revolve around sort of as a prescriber of the erythropoietin-stimulating agents, do you have a sense that they differ in their efficacy?

Clayton Smiley: No. There's no… I have experience with both Aranesp, which we used in the military, and Procrit, which we use here in the private practice setting, and there's really no difference. The one thing that was of benefit as far as Aranesp goes was the prepackaged vials that they came in for patients with chronic kidney disease, but that comes… it's kind of a moot point, because you don't give the prescription at home. It's a very convenient vial to have it come in, but the prescription has to be monitored in the doctor's office, especially with the new FDA guidelines that have come out recently. So, in my experience as a nephrologist over the past 10 years or so, I have not seen any difference in Aranesp or Procrit, as far as achieving the goals that we want to achieve, nor have I noticed any difference in adverse outcomes, and I have no personal experience with the new medication that you approved in March, the peginesatide, or Omontys. I have never prescribed that.

Barak Gaster: Anybody have a question for Dr. Smiley?

Deborah Wiser: This is Deb Wiser. Is it that you have never prescribed because you have not seen a clinical reason to do so, or has there been anything else deterring that?

Clayton Smiley: Right. I have always… we have not… in our group, which is a very large group, we have 21 nephrologists and 3 nurse practitioners, we have a contract with Procrit, so we get a little bit of a less expensive price with Procrit. So, we have never had the opportunity to use it, so I don't have experience with it, just like the military had an exclusive contract with Aranesp when they were able to get a less expensive price for that drug. The efficacy, though, between the two drugs and the adverse outcomes between the two drugs are exactly the same.

I always prefer to give whatever is going to be less expensive, as long as it's noninferior to the patient. They don't require any… the selling point that the Aranesp reps will give to you is that you don't have to dose it as often, and I have not seen in my experience with Procrit that that has even born any fruit. You can dose Procrit once a month in many of my patients and it's not a problem at all.

Barak Gaster: Excellent, thank you, very much. So, this is Barak Gaster. So, this is going to just come down to what the best price that Washington State Medicaid fee-for-service program can get for these 100 patients, so I don't know that we can tell you that one drug should be on the formulary and the other two shouldn't without knowing sort of what that cost will be.

Donna Sullivan: So, this is Donna Sullivan. I have a question, Dr. Smiley. So, when you were saying that you look at using the least expensive drug, is there a way that your clinic compares the cost of these? Are you looking at a cost per unit or cost per week?

Clayton Smiley: That's how we do it is basically a cost per unit and when our contract comes up for renewal we ask both drug companies to be able to come with an opportunity to give us that best price and whoever can give us the best price is who we go with, and so far it's consistently been Procrit because we're such a big group. They're able to give us a good price because they want… the company gives us an economy of scale

to be able to do that, so we are able to get that less expensive price, and whatever Washington State can do to get the less expensive price, you're not going to have any decrease in quality of care to the patient regardless of which drug you choose whether it's Procrit or Aranesp. In my opinion, they're exactly the same.

Donna Sullivan: So, how would you describe a unit of Aranesp compared to a unit of Procrit, because the Aranesp is strength in micrograms where the Procrit and Epogen are in units.

Clayton Smiley: Right. It's… I think it's on page three. I don't know the exact comparable cost, but I believe that the initial dose for Procrit is, as it says right there, 150 units per kilogram subcutaneous three times a week. That's for cancer, excuse me. Let me go down to what I'm more familiar with, which is chronic kidney disease. That is on page…

Donna Sullivan: Seven.

Clayton Smiley: Yeah, seven. So, it's… for people that are on dialysis, it's the same. It's 50 to 100 units per kilogram. Typically, if you give the medicine subcutaneous, the medicine can last a little longer, because it has a depo effect in that you don't have to give it as often, but for people that are on dialysis, the dialysis companies have not gone to giving them subcutaneous shots, just because it's more convenient for the patient to give it IV, so they don't have to have the shot, but obviously in the clinic we give it subcutaneous. I guess the reasoning for not giving it subcutaneous on dialysis also is they get poked with very large needles already to get access to their blood when they're being put on the machine. I think the equivalent dosing, as far as… so it's 50 to 100 units per kilogram for people that are not on dialysis on page seven for Epogen, and it's 0.45 micrograms per kilogram. So, that's the equivalent dosing right there, as far as what is efficacious. Both companies have guideline recommendations to switch from their competitor drug to their own drug. So, Procrit will have a dosing guideline to switch from Aranesp, and Aranesp will have a dosing guideline to switch from Procrit, so that's how you could compare unit to microgram.

Donna Sullivan: Okay.

Barak Gaster: Dr. Smiley, this is Dr. Gaster again. Do you have a ballpark number of clients that are served by your 21 nephrologists?

Clayton Smiley: Oh gosh. It's in the hundreds if not over… it's definitely in the hundreds if not more close to… we have over 1,000 dialysis patients that we care for in our group, and I would presume that the number of chronic kidney disease patients would be larger than the number of dialysis patients that we serve that are on Procrit. I would say it's in the high hundreds range if not over 1,000, but I don't know that number for sure. Let me see if I can text my… while I'm talking right now I'll text Jonlin Horsephal who is our human resources person, and she may have that information. So, I can get that to you. It's in the several hundred.

Barak Gaster: This is Barak Gaster. I'm just trying to put this into context for us in that we're talking about in the ballpark of about 100 patients on Washington State Medicaid fee-for-service that we would be contracting for. So, this is a small group when the manufacturers are looking at our contract. This is going to be a relatively small contract, so I am not sure that we're going to be able to make a super strong decision today based on the data that we've got. So just sort of going back to the apples-to-apples look that we were trying to do that if you look at the cost per claim for patients on getting it for renal failure with dialysis comparing to Aranesp versus Epogen versus Procrit and we're looking at $463 per claim versus $662 per claim versus $492 per claim. It's going to be hard to really get a sense from this data.

Donna Sullivan: This is Donna Sullivan. So, based on the comments from Dr. Smiley, similar to the growth hormone, I can go back and break this down to a cost per unit per kilogram so we can look at the cost per microgram per kilogram in equivalent doses of what it would be moving forward and readdress this next time.

Barak Gaster: Great. And this is Barak Gaster. So, these are all costs that have come about without any negotiating of contract.

Donna Sullivan: That is correct. So, this is the cost, what we've actually paid the pharmacies or the provider minus the federal rebates for the Medicaid program, and I can do this, the cost per milligram per kilogram for

treating chemotherapy, as well, and that will help, I think, if you want to address it for that.

Susan Rowe: This is Susan Rowe. Dr. Smiley, would you say… you're saying these drugs can't be given at home, and they're really tied to monitoring within your office for chronic kidney failure and dialysis. Could we make the same supposition about administration for chemotherapy?

Clayton Smiley: Absolutely. Patients with these medications should not be giving it themselves without monitoring, because all of the studies, the Choir Study, the Treat Study, there was a study that… the Choir Study and the Treat Study were done for patients not on dialysis with chronic kidney disease, and there was another study that was done in the 90s for dialysis patients, and all-cause mortality and strokes were much higher, well not much higher but higher in people where you gave… tried to normalize their hemoglobin. So, it has to be monitored. We're very careful about monitoring them so that no adverse effects, such as a stroke, heart attack, DVT, worsening blood pressure or anything like that could come about. So, I would assume that the oncologists are doing the same thing based upon the new FDA guidelines, yeah.

I don't think you should ever have someone giving it at home, or if they do give it at home because they are in a rural area, they should have their labs done on a weekly basis or semi-monthly basis before the medication is given so that you know the dose, because if the hemoglobin goes too high, you have to either reduce the dose or stop the dose and let the hemoglobin drift back down.

Susan Rowe: This is Susan Rowe. I have one more question. So, given that sometimes the chemotherapy cycles are longer than, you know, people get dialysis more often than maybe the chemotherapy cycles. Would you see any advantage to Aranesp over the shorter-acting agents in that case?

Clayton Smiley: No, because all you have to do is you just have to increase the dose of the Procrit or the Epogen, and it works the same way. I have not seen in my clinical experience that the claim of a longer-lasting medication really pans out in the clinical setting with respect to Aranesp being the "longer-lasting" medication.

Barak Gaster: This is Barak Gaster. We had another question for you that is sort of farther afield and probably not what you were prepared to talk about at all, which was the just before discussing the ESA drug class, we had a discussion about the growth hormone drug class and one of the indications for growth hormone that came up in our discussion was the use of growth hormone for treatment of chronic kidney disease, and we are wondering if you had any thoughts to share for us on the use of growth hormone for treating chronic kidney disease?

Clayton Smiley: Chronic kidney disease specifically? The only time that I have ever heard of or known about growth hormone in a nephrology type of perspective is in pediatric nephrology where they give growth hormone at times to patients… to children with pediatric… pediatric children for transplants. I have never, ever given, nor have I ever even considered giving growth hormone to an adult chronic kidney disease patient.

Barak Gaster: Great.

Clayton Smiley: Or a dialysis patient. That's not been something that I have done or that I'm familiar with, as far as dosing. In all my medical training, unless it's like cutting edge brand new stuff that I… hasn't filtered…

Barak Gaster: This is Barak Gaster. The data that was presented to us was really open-label data on using it in children with chronic kidney disease and growth failure.

Clayton Smiley: Yeah, that's where I am familiar with hearing about it, but I have never prescribed it, since I'm an only an adult nephrologist, so I can't comment clinically as far as the experience goes, but I do know that it is used in that particular way, but I can't comment specifically on cost versus benefit ratio in those patients.

Barak Gaster: Great. Thank you, very much. Any other questions for Dr. Smiley? Great. We thank you again for joining us this afternoon, and we appreciate greatly your time.

Clayton Smiley: Not a problem. Best of luck to you guys in making your decisions, and if there's anything I can do to help you out further, please don't hesitate to contact me.

Barak Gaster: Great. Thanks, again.

Clayton Smiley: Thank you.

Barak Gaster: Alright, so this is Barak Gaster, and we are yet again at a point of really needing more information about this drug class and understanding what the cost per unit will be before deciding whether we can make a formulary decision.

Chuck Agte: This is Chuck Agte, and I would like to ask a general question, because part of our approach originally to the cost analysis, there's a couple of reasons behind the way it's gone this direction and now that we're seeing some of it, why it might not be working out. So, I wanted to ask some guidance there because originally, there's a couple of factors there, one is that with a lot of these drugs with variable dosing, dosing frequency, etc., our original intent was that by looking at the utilization across the board in the manner we've been trying to present it, that we might be able to even out some of the differences in dosing, dosing regimens, etc., but also some of our planning in regards to this was, at the same time… when we first started moving forward with the formulary was at the same time that the agency was moving forward with transitioning clients into managed care.

So, what may have been a more usable approach when there was a larger client set to distribute it across may not be panning out, based on what we're seeing in the data now.

Another reason is that if we do take it down to a per unit comparison for you, that's not something that we can actually… we'll have to look at how we can present that to you, because spreading it out across claims and general utilization allowed us to avoid the issue that revealing federal rebate information is not something that we can do. So, once you get down to a per unit cost, since people know what our payment algorithm is, if you see a per unit cost you can just go oh, well the AWP is this, and therefore if they're saying the per unit cost is that, then here's the federal rebate on that product. So, we have to be careful about information that may reveal federal rebate information. So, we will have to come up with a way to present it potentially as relative costs.

Donna Sullivan: And I think we can definitely present it in relative costs to the committee. Thank you, Chuck. I didn't think about that when I said that we could get it at that level of data.

Chuck Agte: So, I guess my question is now that we're seeing, especially in these drug classes where some of the remaining utilizers within the fee-for-service population don't present enough spread in utilization, what the board would prefer. Also, part of that approach was also we know that Medicaid with some of the sickest population often you also see some of the most variants in prescribing and utilization, and we wanted to try and get a picture of how it was actually being used, you know? For example, if you say this drug costs this per unit and it's dosed this way according to the FDA indications, but if for our clients set, everyone always receives double that dose, that was part of what this tried to get to. Does the board see a benefit in that, or are we at this point looking at the most value to you generally being some kind of comparative per unit cost for most classes? So, we'd like your guidance on… because we don't want to keep producing data analysis that may not be something that you can base a decision on.

Donna Sullivan: And what I would like to do is, we can drill it down into the units per claim so that you know kind of if one drug is being prescribed, you know, kind of outside of the recommended guidelines, the labeled guidelines, and then we could give you relative costs in patients. So, we can break it down to a more granular level and then provide you with the unit cost, which I think will help us identify if these are being prescribed slightly differently than what the labeling indicates is appropriate.

Barak Gaster: This is Barak Gaster. I don't think that there is one answer that is going to work for every drug class, and I think that these last two that we've done, the growth hormone and the epo agents are, you know, they're just kind of weird, unique, expensive drugs that are used in weird ways with not that many clients that it's going to be just hard. It's going to be, you know, in both cases we came to the conclusion that all the drugs in the classes are pretty interchangeable. So, really it kind of comes down to whatever is going to be the cheapest for Washington State Medicaid fee-for-service program. So, I would say

present whatever data that you can provide to us that helps us to project what that cost will be… what those costs will be.

Donna Sullivan: Absolutely.

Barak Gaster: I don't think, so far, we've seen data that really allows an accurate projection in that way to make a formulary decision. So, as of now, we feel kind of stuck in being unable to really sort of build a formulary for either of these drug classes.

Chuck Agte: Chuck Agte. That's understandable. So, I would still like to redirect the board and comment on some of the input that we've received on Omontys. Just so the board knows, part of the reason… we've actually been looking at reconsidering that criteria for a little while, but because we already had this class scheduled in front of the board, we thought it best to go ahead and defer to the board who is reviewing the class anyway. We did not change our criteria internally, because at least at the time we started to look at it, it was going to be in front of the board soon, and then I think that got delayed and then we had to defer it once it was actually in front of the board, but the original intent was this was coming to the board anyway, and we wanted to let the board make a decision. So, I would request, if the board is able, to go ahead and advise on that criteria for Omontys, even if we are deferring the class, because we don't want to continue to defer a possible necessary change in our criteria if you guys deem that appropriate, because if we continue to put this class out, it continues to potentially unnecessarily defer what is our PA criteria in the meantime.

Donna Sullivan: This is Donna Sullivan. I do want to say one thing though. Right now, we haven't covered any of the Omontys under the current criteria. I'm not sure it would make sense to change our policy at this time and allow patients to start on a medication that may become non-formulary in February or that you may become, you know, make non-formulary in the future and then have to go through another change. So, I just want to keep that in mind, for any recommendation.

Barak Gaster: So, this is Barak Gaster. I'm just looking at the conclusion in the monograph that we reviewed at our last meeting, which just says that Omontys provides the added benefit and convenience of once-monthly dosing but all available ESAs, including Omontys, are considered

equally safe and effective based on indication and differ only in dosing frequency and cost.

So, I don't think we have heard anything here at this committee that sort of calls out Omontys as being dramatically different. We have no idea how much it costs. So, for that reason, we're a little bit weary. We have some sense that Aranesp, Epogen, and Procrit are all equally very expensive, and we would imagine that Omontys is also very expensive. We don't know that it might not be even much more expensive than these three. So, that, I think, is our only concern, because it's the data that we are lacking, but in terms of its safety and efficacy, I don't think we've heard anything that makes us concerned that it is less safe or less effective or more safe or more effective than the other three drugs that we've reviewed.

So, unless you have something that makes you concerned that it is going to be much more expensive, placing added barriers to Omontys relative to the other three drugs in the class, probably doesn't make a lot of sense.

Chuck Agte: And this is Chuck Agte. No, it was not… for that particular advice of the board, we're not looking for cost comparison, because it was a clinical decision at the time based on potential perceived safety issues and getting a new drug on the market.

Barak Gaster: Right.

Donna Sullivan: And this is Donna Sullivan. The other thing is, we don't know. It may be less expensive. So, when I bring back the cost data, I will do the best I can to, using our algorithm, try to cost out what we think it would cost us to have Omontys on as a formulary agent so that you can look at that, because it wouldn't make sense to keep excluding it if it was actually less expensive than the alternative.

Barak Gaster: So, this is Barak Gaster. I think I can speak for the board that we have not heard any safety concerns that would call it out as separate from the rest of the drugs in the class.

Chuck Agte: Thank you.

Christopher Smith: So, Donna, Christopher Smith. In terms of this cost estimate, the units of the medications are different, the dosing intervals are different so you'll have an equivalent effectiveness per month?

Donna Sullivan: Yes.

Christopher Smith: Is that basically how you're going to come up with it?

Donna Sullivan: Yes.

Christopher Smith: How it would be used clinically, on average, not necessarily with a couple of extreme clients that dosed it either very high or very low.

Donna Sullivan: Correct, and what I will do is I will give you the per unit cost of what it would cost on the average dose per month, as well as how it's being used in our population, so we can give you the units per month that are actually being used among our population.

Barak Gaster: Alright, so with that, I think we can adjourn today's meeting.

Donna Sullivan: I do have one… we do need to talk about what we're going to look at in February.

Barak Gaster: Alright. Let's do that.

Donna Sullivan: In February, we will be getting back to some preferred drug classes, so we won't be doing 100% formulary. So, I'm hoping to bring… there's the newer anticoagulant drugs, there's a summary update that has been done on those products, as well as a scan on the DPV-4 inhibitors and the new drug linagliptin. I think there's a drug addendum on that, and there's a couple of other scans that I'm checking out to see if we'll be bringing those. So, most of the morning session in February will be preferred drug list, and then for the DUR portion, we'll relook at the growth hormones, the ESA population. There's interest in looking at the anticonvulsants, because it is one of our highest cost drug classes, pulmonary arterial hypertension, and then possibly COPD drugs.

We're running into squishing into agenda time, because I also want to look at the top 20 opioid prescribers. Unfortunately, I had a lot of questions about the data when I got it that I wasn't able to get

answered, so I didn't want to present to that to the board before I had those questions. So, I'm thinking that I'll try to narrow that down to the growth hormones, ESAs, possibly one other drug class, and then the opioid presentation for the day.

Susan Rowe: This is Susan Rowe. Donna, on the pulmonary hypertension, we're going to need someone else to be calling in.

Donna Sullivan: I figured that.

Susan Rowe: We're going to need a helper.

Donna Sullivan: Okay.

Susan Rowe: Thank you.

Donna Sullivan: And I don't know if you guys would know, would that be a cardiologist versus a pulmonologist or both? Pulmonologist?

Barak Gaster: Pulmonologist.

Donna Sullivan: Okay.

Chuck Agte: This is Chuck Agte. Along the same lines, for any of the other drug classes mentioned, do you feel a need for additional input on any of the others, just to double check?

Donna Sullivan: With the anticonvulsants, the monograph that we have from MedImpact, it focuses more at seizure disorder, as opposed to mood stabilizer use. So, I think we would be narrowing the indications on seizure disorder. So, if you like, if we do bring that, I will try to get the appropriate neurologist, epileptic specialist on the phone.

Barak Gaster: That would be great.

Donna Sullivan: And if I can't find a specialist, then we won't be looking at those drugs.

Barak Gaster: Perfect. Thank you. Great. Alright, this is Barak Gaster. I want to wish everyone a Merry Christmas and Happy New Year, and thank you very much.